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TITLE: Early ICU Standardized Rehabilitation Therapy for the Critically Injured Burn Patient

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
This is a multicenter, randomized controlled trial to determine whether early ICU rehabilitation, for Burn Intensive Care Unit (BICU) patients will decrease hospital length of stay. 50 subjects will be randomized at each of three sites for a total of 150 subjects. The study has completed all regulatory requirements, completed site protocol developments and has begun to enroll patients. The goal enrollment minimums are an average of 2.5 patients enrolled per month, per site; 7.5 patients enrolled per month, across the study. This study will increase understanding of the effect of rehabilitation on ICU Burn patients, through ultrasound and strength assessments of muscles, performed at study entry (ultrasound), ICU & Hospital discharge and at 3, 6 and 12 months (ultrasound & strength assessments) post-enrollment. Functional testing with Short Physical Performance Battery (SPPB) and Health Related Quality of Life (HRQoL) testing will determine if standardized early rehab improves functional performance, quality of life and employment status.
Accomplishments Year #1: Database build, design web entry case report forms, site training; finalized IRB consent forms and began enrollment, 3 subjects to date, with outpatient follow-up 3, 6, and 12 month sessions planned.
Accomplishments Year #2: Active Study with enrollment of study subjects at all three sites. Completion of training of ultrasound techniques at all three sites. Out-patient follow-up has begun for those enrolled within the first year of the study.

15. SUBJECT TERMS
Critical Injury, Burn Patient, Rehabilitation Therapy

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PROJECT:
Early ICU Standardized Rehabilitation Therapy for the Critically Injured Burn Patient
Annual Report
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Introduction:

This project was originally funded in order to conduct a multicenter, randomized controlled trial to determine whether early ICU rehabilitation, for Burn Intensive Care Unit (BICU) patients, would decrease hospital length of stay. The original protocol specified fifty subjects to be randomized at each of three sites for a total of 150 subjects. Study start-up was initiated in Year #1 and all sites began to enroll patients. Twenty-three study subjects were been enrolled. Out-patient visits during the post-enrollment, post-hospital discharge phase of the study were also initiated and the outpatient phase of testing was instituted. The sites were committed to increasing enrollment goals to match above planned – and the enrollment did show a tick upwards in the last year that the protocol was active.

This study however did receive great discussion across the investigators due to a recently completed similar study that was administered within a medical ICU population. The results of the medical ICU early rehab study are reviewed below and the subsequent steps taken by the PI's are as well described. That particular medical ICU population study has been published recently and appeared in JAMA.

Keywords:

Burn Injury, Critical Care, Intensive Care, Standardized Rehabilitation Therapy

Overall Project Summary:

Monthly study conferences were conducted with discussion across PI's and coordinators. These conferences led to recommendations addressing enrollment volume within the study. These conversations were detailed and examined possibilities at each site to identify improvements in process.

Patient screening and patient enrollment:

Patient screening was ongoing at all three sites.

Patient review:

To date, twenty-three study subjects were enrolled. Appropriate timelines were adhered to in regards to study enrollment windows. Appropriate execution of study inclusion and exclusion rules was conducted. Each study subject had an appropriate study IRB consent form, with appropriate dated signatures, obtained prior to randomization. Randomization procedures were engaged and functioned without difficulty.

To date both study arms were engaged with study subjects. Standardized rehabilitation therapy and usual care were delivered to study subjects. Success was achieved in the delivery of multiple intervention arm rehabilitation sessions including delivery of resistance training exercise with Therabands. Blinded exercise physiologists had conducted the strength and functional assessments according to protocol.

Key Research Accomplishments:

- All IRB and HRPO obligations were met

- All subcontract sites had working relationships with Wake Forest to receive study payments

- All payments on this grant mechanism have been put on hold and have been on hold since April 29th, 2015, when Dr. Morris moved from Wake Forest to the University of Kentucky (see below for subsequent plans to continue with this award).

- Electronic secure remote entry database was functioning

- SUMMARY OF CHANGES WITHIN ORIGINAL STUDY:

Two observations led the Principle Investigators to reconsider the design and execution of the original study, "Early ICU Rehabilitation Therapy for the Critically Injured Burn Patient". The original study set out to examine the effect of early intensive rehabilitation compared with usual care in severely burned patients.

The first observation included the results of a recently concluded Medical ICU Early Rehab study. This Medical ICU Rehab study failed to demonstrate an effect on prespecified in-hospital study endpoints. Extrapolating from these findings, the investigators seriously considered that Medical ICU trial's data to help predict the Burn Rehab Study outcome. The investigators now hold that it is unlikely that a treatment effect will be observed in the Burn Rehab study, even with full burn patient trial enrollment. Thus, an argument for halting the study for reasons of futility was developed and carried out.

The second observation arose directly from the Burn Rehab study itself. The Burn Rehab study's observation was a commonly occurring patient care delivery pattern within the severely burned patient population. This second observation was managing the protocol in light of frequent trips to the operating room. That is, the necessity of frequent planned operative interventions for the purposes of burn wound debridement, soft tissue coverage or related procedures often precluded delivery of the rehabilitation protocol. These multiple planned surgeries often disrupted scheduled rehabilitation sessions in patients randomized to the early, aggressive intervention arm of the Burn Rehab study. Specifically, because of these multiple operations, patients would often be too sedated to participate in prescribed rehabilitation therapy, would be about to go to the operating room or would be unavailable for participation because the scheduled rehabilitation session conflicted with the patient's operation.

The disruptive effect of the multiple operating room trips was by nature a characteristic of a burn population. Such operating room trips however, were not previously encountered when the rehabilitation intervention was studied in medical ICU patients (which served as the prototype for the study conducted in burn patients). Thus, such a need to account for the volume of operating room trips was not formulated into the original Burn Patient study design.

Collectively, the two observations resulted in the original study being placed on administrative hold and then closed. Enrollment in the "Early ICU Rehabilitation Therapy for the Critically Injured Burn Patient" has been terminated by the Principle Investigators. This step was undertaken to allow for reconfiguration and refocus of the investigative effort and resources. A new set of tasks were then designed within the original Scope of Work addressing the frequent operative needs of Burn patients and are presented here.

In the new phase of this current grant award, we will design a completely new Burn population Rehab study structure through a national database review. We propose to examine medical records within a large national hospital database (University Hospital Consortium's database) to identify optimal care delivery patterns reflected by outcome analysis. A barrier to the rehabilitation efforts within the original study's intervention arm was the immobilization of the critically ill patient, whether due to the injury or as a side effect of supportive care. Minimizing the duration of this immobilization and developing strategies to lessen its impact are the goals of this proposed continuation plan. To the extent that periods of immobility are due partly as a consequence of variability in operative practice, understanding and minimizing such variability has the potential to translate into more timely recovery of the severely injured patient, including those sustaining burns.

Thus, critical to the effort of revising our investigative, interventional approach, is this proposal of the 2nd Phase of this study. This 2nd Phase of the Study will develop a deeper understanding of clinical factors surrounding the “repetitive and re-look” procedures within the Critically Ill Burn Patient Population. In this final phase of the current award, the UHC database review study will increase the medical literature's understanding of what contributes to variability in practice surrounding the care of burn patients with conditions necessitating multiple planned operations. This insight will be essential to the future design and execution of a revised Burn ICU Rehabilitation study (a future grant application). The optimal future design will more effectively coordinate interventions among and across critical care, surgical, nursing, physical therapy, respiratory therapy and related disciplines.

Accordingly, the investigators feel that the proposed continuation plan will both fall within the scope of work of the original proposal and will be essential to developing strategies to optimizing the care of the severely burned patient.

One model system for studying the phenomenon of variability in practice in the setting of multiple planned operations is need to have critically ill burn patients return to the operating room. The concept of return to the operating room for burn surgical therapies was developed as a management strategy for patients in which the constellation of injuries precludes definitive repair at the time of ICU admission or index operation, when the patient is not sufficiently stable to tolerate a definitive operation, when there is concern that all injuries may not be accurately identified at the index operation, or in an effort to stage the needed surgical therapy.

Subsequently, use of this strategy has become more commonplace and applied along local practice rather than national standards. As a result, use of return procedures to the operating room for burn patients has variability with both institutions and practitioners. The more extensive the burn injury, the higher comorbidities or a greater number of related injuries or organ dysfunctions, then there will be a corresponding population of burn patients with greatest volumes of operating room visits. These needs for multiple operating room visits may correlate with longer duration of mechanical ventilation, greater intensive care unit (ICU) and hospital lengths of stay (LOS), and higher utilization of operating room resources. In turn, because of this prolongation of hospitalization, these patients also appear at increased risk of complications. Adding to and confounding variability in the return to the operating room, is potential lack of availability of operating room resources to accommodate multiple operations and inconsistency in patient management between operating rooms sessions (such as approaches to ventilator weaning, sedation, and mobilization). Cumulatively, this variability translates not only into increased resource expenditure but poses a barrier to early rehabilitation and restoration of function.

Our overarching hypothesis of the 2nd Phase of this grant award is that variation in practice among patients requiring planned repetitive operative therapy negatively impacts resource utilization and treatment of critically ill burn patients. Efforts to standardize these aspects of care have potential to more effectively target rehabilitative interventions in the setting of burn patients.

Conclusion:

Our 2nd Phase proposal consists of three highly interrelated specific aims:

In Specific Aim 1, we will utilize highly granular administrative databases to demonstrate and quantify inter-institutional variability in a model system - use of return to operating room procedures in critically ill burn patients.

In Specific Aim 2, we will utilize the information obtained in SA1 as a foundation for developing a standardized approach to planned return operating room procedures for critically ill burn patients.

In Specific Aim 3, we will adapt and synthesize a written pilot approach developed in SA2 to optimizing rehabilitative care in patients sustaining significant burn injuries and who require multiple planned operative interventions.

Publications, Abstracts, and Presentations:

a. Manuscripts:
    1. Lay Press:
    2. Peer-Reviewed Scientific Journals:

Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, Dhar S, Chmelo E, Lovato J, Case LD, Bakhru RN, Sarwal A, Parry SM, Campbell P, Mote A, Winkelman C, Hite RD, Nicklas B, Chatterjee A, Young MP. Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. JAMA. 2016 Jun 28;315(24):2694-702. doi: 10.1001/jama.2016.7201

Jolley SE, Moss M, Needham DM, Caldwell E, Morris PE, Miller RR, Ringwood N, Anders M, Koo KK, Gundel SE, Parry SM, Hough CL. Point Prevalence Study of Mobilization Practices for Acute Respiratory Failure Patients in the United States. Critical Care Medicine, 2016 in press. DOI: 10.1097/CCM.0000000000002058

Balas M, Devlin JW, Verceles AC, Morris P, Ely EW. Adapting the ABCDEF Bundle to meet the needs of patients requiring prolonged mechanical ventilation in the long-term acute care hospital setting: historical perspectives and practical implications. Semin Resp Crit Care Med 2016: 37:1-17

Files DC, Sanchez MA, Morris PE. A conceptual framework: the early and late phases of skeletal muscle dysfunction in the acute respiratory distress syndrome. Crit Care. 2015 Jul 2;19:266. doi: 10.1186/s13054-015-0979-5

3. Invited Articles:

4. Abstracts:

Point Prevalence Study of Intensive Care Unit Mobility Across the Acute Respiratory Distress Syndrome Network. Sarah E. Jolley, Marc Moss, Dale M. Needham, Ellen S. Caldwell, Peter E. Morris, Russell R. Miller, Nancy Ringwood, Megan G. Anders, Karen Koo, Selina M. Parry, Stephanie Gundel, Catherine L. Hough, A104. MOVING THE NEEDLE ON ICU-ASSOCIATED NEUROMUSCULAR WEAKNESS, 2015: A6349, 10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A6349

Feasibility of Fall Risk Assessments Within Acute Respiratory Failure Survivors with the Falls Efficacy Scale-International. Selina M. Parry, Rita N. Bakhru, Daniel C. Files, Sanjay Dhar, Michael T. Young, Lori Flores, J Lovato, Jordan Hauser, Elizabeth A. Chmelo, P Mote, Clifton Thompson, Pam Campbell, Linda Denehy, L Case, Michael J. Berry, Peter E. Morris, C47. SURVIVING SEPSIS: MANAGING THE CARE CONTINUUM, 2015: A4495, 10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A4495

Metabolomic Analysis of the TARGET Cohort Identifies Serum Signatures That Outperform Lactate in Sepsis Prognosis. Raymond J. Langley, , Lori Flores, Robert Mohney, J Lovato, L Case, Kevin S. Harrod, Peter E. Morris. C23. SEPSIS: RISK, RECOGNITION, AND RESUSCITATION, 2015: A4007, 10.1164/ajrccm conference.2015.191.1 Meeting Abstracts.A4007

The Design and Implementation of a MICU Survivors' Clinic: A Fellow's Journey Starting from Square One. James Davidson, Daniel C. Files, Rita N. Bakhru, , Kristin Griffin, Peter E. Morris. C47. SURVIVING SEPSIS: MANAGING THE CARE CONTINUUM, 2015: A4499, 10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A4499

Cardiac and Skeletal Muscle Dysfunction in an Aging Mouse Model of Acute Lung Injury. Michael A. Sanchez, , Chun Liu, Jasmina Varagic, Peter E. Morris, Daniel C. Files. A57. LUNG INJURY, REPAIR, AND FIBROSIS: THE PLOT THICKENS FOR THREE'S COMPANY, 2015: A2054, 10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A2054

Love NJ, Morris PE, Case LD, Lovato J, Berry MJ. Relationship Between Self-Report and Performance Based Measures of Physical Function Following an ICU Stay. Med Sci Sports Exerc. 2016 May;48(5 Suppl 1):282. doi: 10.1249/01.mss.0000485849.11592.a1.

b. Presentations: by Peter Morris, MD (PI)

1. October 2015, Brisbane Australia, National Annual Meeting of the Australia Physiotherapist Association, New Paradigms for Early ICU Rehab

2. October 2015, University of Melbourne, Update on Early ICU Rehabilitation

3. October 2015, The Albert Hospital, Melbourne, Australia, Clinical Review of ICU Rehab Techniques

4. November 2015, Medical Grand Rounds, The Cleveland Clinic, Cleveland, Ohio, The Message From Recent Clinical Trials in Early ICU Rehabilitation Studies

Inventions, Patents, and Licenses:

Nothing to report

Reportable Outcomes:

Nothing to report

Other Achievements:

Nothing to report

Appendices:

Manuscript and abstract publications

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure
A Randomized Clinical Trial

Peter E. Morris, MD; Michael J. Berry, PhD; D. Clark Files, MD; J. Clifton Thompson, RN; Jordan Hauser, MS; Lori Flores, RN; Sanjay Dhar, MD; Elizabeth Chmelo, MS; James Lovato, MS; L. Douglas Case, PhD; Rita N. Bakhru, MD, MS; Aarti Sarwal, MD; Selina M. Parry, PhD; Pamela Campbell, RN; Arthur Mote; Chris Winkelman, PhD; Robert D. Hite, MD; Barbara Nicklas, PhD; Arjun Chatterjee, MD, MS; Michael P. Young, MD

IMPORTANCE Physical rehabilitation in the intensive care unit (ICU) may improve the outcomes of patients with acute respiratory failure.

OBJECTIVE To compare standardized rehabilitation therapy (SRT) to usual ICU care in acute respiratory failure.

DESIGN, SETTING, AND PARTICIPANTS Single-center, randomized clinical trial at Wake Forest Baptist Medical Center, North Carolina. Adult patients (mean age, 58 years; women, 55%) admitted to the ICU with acute respiratory failure requiring mechanical ventilation were randomized to SRT (n=150) or usual care (n=150) from October 2009 through May 2014 with 6-month follow-up.

INTERVENTIONS Patients in the SRT group received daily therapy until hospital discharge, consisting of passive range of motion, physical therapy, and progressive resistance exercise. The usual care group received weekday physical therapy when ordered by the clinical team. For the SRT group, the median (interquartile range [IQR]) days of delivery of therapy were 8.0 (5.0-14.0) for passive range of motion, 5.0 (3.0-8.0) for physical therapy, and 3.0 (1.0-5.0) for progressive resistance exercise. The median days of delivery of physical therapy for the usual care group was 1.0 (IQR, 0.0-8.0).

MAIN OUTCOMES AND MEASURES Both groups underwent assessor-blinded testing at ICU and hospital discharge and at 2, 4, and 6 months. The primary outcome was hospital length of stay (LOS). Secondary outcomes were ventilator days, ICU days, Short Physical Performance Battery (SPPB) score, 36-item Short-Form Health Surveys (SF-36) for physical and mental health and physical function scale score, Functional Performance Inventory (FPI) score, Mini-Mental State Examination (MMSE) score, and handgrip and handheld dynamometer strength.

RESULTS Among 300 randomized patients, the median hospital LOS was 10 days (IQR, 6 to 17) for the SRT group and 10 days (IQR, 7 to 16) for the usual care group (median difference, 0 [95% CI, −1.5 to 3], *P*= .41). There was no difference in duration of ventilation or ICU care. There was no effect at 6 months for handgrip (difference, 2.0 kg [95% CI, −1.3 to 5.4], *P*= .23) and handheld dynamometer strength (difference, 0.4 lb [95% CI, −2.9 to 3.7], *P* = .82), SF-36 physical health score (difference, 3.4 [95% CI, −0.02 to 7.0], *P*= .05), SF-36 mental health score (difference, 2.4 [95% CI, −1.2 to 6.0], *P* = .19), or MMSE score (difference, 0.6 [95% CI, −0.2 to 1.4], *P* = .17). There were higher scores at 6 months in the SRT group for the SPPB score (difference, 1.1 [95% CI, 0.04 to 2.1, *P* = .04), SF-36 physical function scale score (difference, 12.2 [95% CI, 3.8 to 20.7], *P* = .001), and the FPI score (difference, 0.2 [95% CI, 0.04 to 0.4], *P* = .02).

CONCLUSIONS AND RELEVANCE Among patients hospitalized with acute respiratory failure, SRT compared with usual care did not decrease hospital LOS.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00976833

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Acute respiratory failure is associated with high mortality and prolonged morbidity, with impaired physical function for many survivors. Interventions directed at attenuating the profound muscle wasting in patients with acute respiratory failure are patient-centered.[1] Such therapies designed to improve patient-reported weakness and impaired physical function could reduce recovery time in patients with acute respiratory failure. As well, such interventions could potentially improve long-term health-related quality of life, which for this population is commonly below normal following hospital discharge.[2-4] Reports have suggested that a rehabilitation program, delivered by an intensive care unit (ICU) rehabilitation team, may be associated with reduced length of stay (LOS) and improved physical function, although findings to the contrary exist as well.[5-11] This randomized clinical trial was designed to test the hypothesis that early delivery of a standardized, multifaceted ICU and hospital rehabilitation program would decrease hospital LOS and improve physical function for patients with acute respiratory failure.

Methods

Study Design and Oversight

The institutional review board at the enrolling hospital approved the clinical trial. Written consent was obtained from participants or their legally authorized representative. Race and ethnicity data were collected per the National Institutes of Health reporting policy and determined by patient or surrogate self-reporting based on fixed categories. The study was a single-center, assessor-blinded, randomized investigation with 2 groups: standardized rehabilitation therapy (SRT) and usual care conducted at Wake Forest Baptist Medical Center in Winston Salem, North Carolina. The SRT group received rehabilitation therapy 7 days a week, from enrollment through hospital discharge, including days spent in a regular floor bed. The usual care group received routine care as dictated by the patient's attending physician from Monday through Friday. SRT ended at hospital discharge. Both groups underwent testing at ICU and hospital discharge, and at 2, 4, and 6 months after enrollment by research personnel blinded to the randomization assignment.

Study Patients

Inclusion criteria were admission to a medical ICU, being 18 years or older, mechanical ventilation via endotracheal tube or noninvasive ventilation by mask, and an arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FIO_2) ratio less than 300. Exclusion criteria were inability to walk without assistance prior to the acute ICU illness (use of cane or walkers were not exclusions), cognitive impairment prior to acute ICU illness described by surrogate, as nonverbal, acute stroke, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) greater than 50, neuromuscular disease impairing weaning from mechanical ventilation, acute hip fracture, unstable cervical spine or pathologic fracture, mechanically ventilated more than 80 hours or current hospitalization (including transferring hospital) more than 7 days, orders for do not intubate on admission, considered to be moribund by the primary attending, or enrolled in another research study.

Randomization

Patients were randomly assigned, using a computer-generated variably sized approach (in block sizes of 2, 4, 6, or 8), to SRT or usual care.

Study Measurements and Procedures

The SRT protocol contained 3 exercise types: passive range of motion, physical therapy, and progressive resistance exercises, and was administered by a rehabilitation team for a total of 3 separate sessions every day of hospitalization for 7 days per week.[6] The team comprised a physical therapist, an ICU nurse, and a nursing assistant. Passive range of motion included 5 repetitions for each upper and lower extremity joint. Physical therapy included bed mobility, transfer training, and balance training. These exercises included transfer to the edge of the bed; safe transfers to and from bed, chair, or commode; seated balance activities; pregait standing activities (forward and lateral weight shifting, marching in place); and ambulation. Progressive resistance exercise included dorsiflexion, knee flexion and extension, hip flexion, elbow flexion and extension, and shoulder flexion. Resistance was added through the use of elastic resistance bands (TheraBand, Hygienic Corporation). Both the physical therapy and resistance training targeted lower extremity functional tasks and activities of daily living (for further details of the implementation of SRT modalities, see trial protocol in Supplement 1).

The patient's level of consciousness determined suitability for receipt of physical therapy or progressive resistance exercise, and ability to complete the exercises.[12] When patients were unconscious, the 3 sessions consisted of passive range of motion. Once the patient gained consciousness, physical therapy and progressive resistance exercise were introduced. Being free from mechanical ventilation was not a prerequisite for any of the exercise sessions. The usual care group received no rehabilitation per treatment protocol. Physical therapy could be ordered as part of routine care, but only Monday through Friday.

Study Outcomes

The primary end point was hospital LOS, defined to include hospital calendar days (or any portion of a calendar day) at the enrolling hospital and at any long-term acute care facility to which the patient was directly transferred. Research team members were not involved in the decision for hospital discharge (ie, the primary end point). Hospital floor medical teams separate from the ICU teams were responsible for hospital discharge. Study days were days of hospitalization following randomization.

Secondary outcomes included physical function and health-related quality of life. Physical function was measured using both performance-based and self-report instruments. Performance-based tests included the Short Performance Physical Battery (SPPB) and muscular strength as determined by handgrip dynamometer (Jamar, Lafayette Instrument) and from a handheld dynamometer (microFET2, Hoggan Health Industries).

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SPPB scores were derived from performance of 3 components: a 4-meter walk, chair sit-to-stand, and a balance test.[13] Muscular strength of the shoulder flexors, elbow flexors and extensors, hip flexors, knee flexors and extensors, and ankle dorsiflexors was measured thrice bilaterally. The maximum values from each test were averaged to produce a single composite value of muscular strength. Self-report tests consisted of the short form Functional Performance Inventory (FPI),[14] and the physical functioning scale of the medical outcomes study 36-Item Short Form Health Survey (SF-36 PFS).[15] Health-related quality of life was measured using the SF-36 physical health survey (SF-36 PHS) and mental health survey (SF-36 MHS) component summary scores and Mini-Mental State Examination (MMSE) score. Measures of physical function were obtained at ICU discharge, hospital discharge and 2, 4, and 6 months after enrollment. Health-related quality-of-life measures were obtained at hospital discharge and 2, 4, and 6 months after enrollment. The SF-36 and the FPI were not administered at ICU discharge as they were not considered relevant to the patient at this time. The FPI was not administered at hospital discharge for the same reason. Post-hoc outcomes were the number of days that patients were alive and breathing without ventilator assistance (ventilator-free days), ICU-free and hospital-free days to day 28.[16] Adverse events were quantified by deaths, device removals, reintubations, and patient falls during physical therapy (for classification of adverse events, see trial protocol in Supplement 1).

Statistical Analysis

The initial plan was to accrue 326 participants to provide 80% power for detecting a 30% decrease in the median hospital LOS at the 5% 2-sided level of significance assuming an exponential LOS distribution, a 20% in-hospital mortality, and that 5% of the remaining patients would withdraw prior to discharge, resulting in 247 discharges.

The projected 30% decrease in the primary outcome (hospital LOS) is slightly larger than the decrease observed in a previous quality improvement report,[6] but, as described below, there was a greater expected effect with the current intervention due to a greater potential for exposure to the SRT after ICU discharge in this study. An important feature of the previous quality improvement report was that the intervention was delivered only in the ICU. Hence, the effect reported was for intervention delivered only in the ICU, not after ICU discharge. Despite the intervention being limited to the ICU, there was a 24% adjusted reduction in hospital LOS (hazard ratio [HR], 1.31). The current study design delivered the SRT from ICU admission through hospital discharge and due to the addition of progressive resistance exercise, there was a much greater clinical effect expected.

The in-hospital mortality and dropout were both less than expected and enrollment was stopped after 300 patients were accrued, 257 of whom were discharged.

Kaplan-Meier methods were used to estimate hospital LOS, and a log-rank test was used to assess the difference between groups. Patients who died or dropped out before discharge were censored in the analyses. A Cox proportional hazards regression model was used to estimate the hazard ratio. Because there were concerns that censoring (particularly from deaths) might be informative, 2 extremes were considered—assuming all the patients who died would have been discharged on the day of their death and that all the patients who died would have had the longest hospital stays. The same assumptions were made regarding the patients who simply withdrew even though there is less reason to believe that those would be informative. Analyses were repeated under the possible combinations of assumptions regarding the deaths and dropouts. For each of these scenarios, unadjusted analyses and analyses adjusted for those variables related to in-hospital death (sex, mean arterial pressure, partial pressure of carbon dioxide [$Paco_2$], Pao_2, Fio_2, and Acute Physiology and Chronic Health Evaluation [APACHE] score) were conducted. χ^2 Tests were used to assess group differences in-hospital and after discharge deaths and Wilcoxon rank-sum tests were used to assess group differences in ventilator-free and ICU-free days. Median differences of medians and 95% confidence intervals were generated using bootstrap methods with 10 000 bootstrap samples. The significance threshold was $P < .05$ for each outcome and testing was 2-sided. Due to the lack of adjustment for multiple testing, the secondary analyses should be considered exploratory. The statistical software was SAS (SAS Institute), version 9.4.

For secondary outcomes assessed longitudinally, a mixed-effects repeated measures analysis of variance model was used to assess differences in these measures between the SRT and usual care groups at discharge, 2, 4, and 6 months. An unstructured covariance matrix was used to account for the within-patient correlation over time.

χ^2 and Wilcoxon rank-sum tests were used to assess differences in patient characteristics between those patients with and without missing data. Those characteristics predictive of missingness (due either to death or withdrawal) were included in the longitudinal mixed models. These covariates included age, race, BMI, ICU diagnosis, mean arterial pressure, $Paco_2$, Pao_2/Fio_2 ratio, APACHE score, and number of comorbid conditions. Multiple imputation was also used to assess the sensitivity of the results to the missing at random assumption. To be conservative, it was assumed that all dropouts would follow a pattern similar to that seen among the control patients (usual care group).[17] One hundred data sets were generated using the SAS MI procedure (SAS Institute), a repeated measures mixed model was run on each data set, and results were combined using the SAS MIANALYZE procedure (SAS Institute).[18] Covariates related to missing data were included in the imputations and in the adjusted mixed models. The imputation analyses included all patients.

Results

Study Patients

From October 2009 through November 2014, 4804 patients with acute respiratory failure were screened, 618 were eligible, and 300 were randomized (**Figure 1**) and followed up for up to 6 months after the enrollment date (last follow-up visit, November 2014). There were 84 patients in the SRT group (56%) vs 81 in the usual care group (54%) who com-

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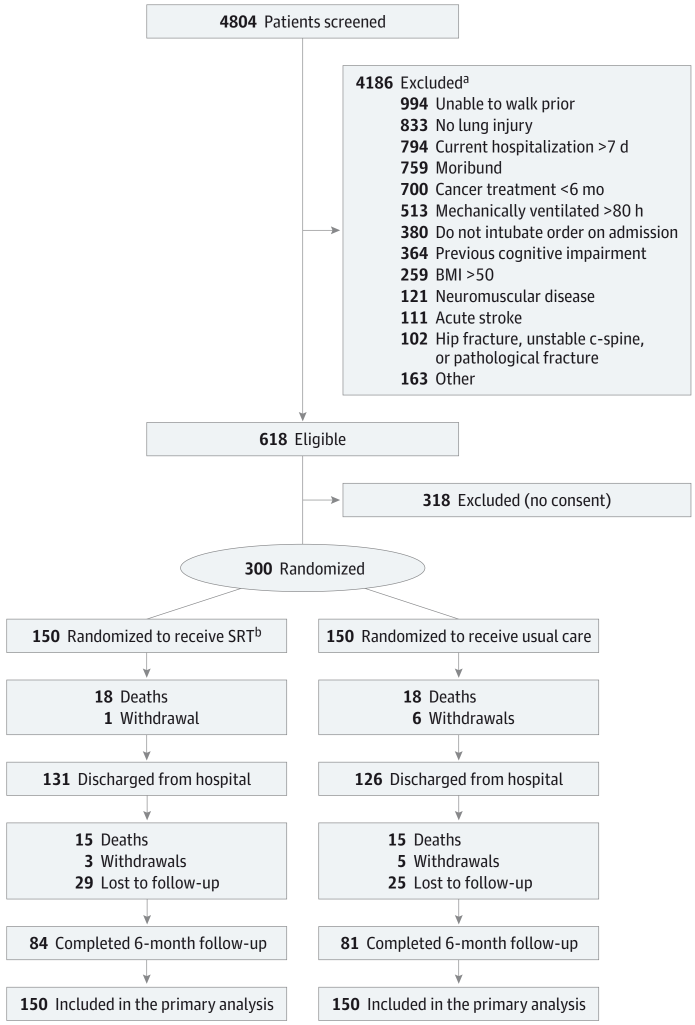
Figure 1. Flow of Patients Through the Study of Rehabilitation for Patients With Acute Respiratory Failure



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); SRT, standardized rehabilitation therapy.

[a] Patients could have more than 1 exclusion. Either patient or surrogate may have provided or refused consent.

[b] One patient after completing intervention was deemed technically ineligible; the patient was consented and randomized to SRT but was found to be unable to walk prior to study and included in the primary analysis.

pleted the 6-month follow-up. There were no clinically important differences in baseline characteristics between the 2 groups (**Table 1**).

Study Interventions

For the SRT group, the median days to first therapy exercise were 1 (interquartile range [IQR], 0-2) for passive range of motion, 3 (IQR, 1-6) for physical therapy, and 4 (IQR, 2-7) for progressive resistance exercise, whereas the days to first therapy exercise for the usual care group were 7 (IQR, 4-10). The mean percentage of study days SRT patients received therapy was 87.1% (SD, 18.4%) for passive range of motion, 54.6% (SD, 27.2%) for physical therapy, and 35.7% (SD, 23.0%) for progressive resistance exercise. The mean percentage of study days usual care patients received physical therapy was 11.7% (SD, 14.5%). For the SRT group, the median days of delivery of therapy per participant was 8.0 (IQR, 5.0-14.0) for passive range of motion, 5.0 (IQR, 3.0-8.0) for physical therapy, and 3.0 (IQR, 1.0-5.0) for progressive resistance exercise. The median days of delivery of physical therapy for the usual care group was 1.0 (IQR, 0.0-8.0).

Primary Outcomes and Hospital Data

The median hospital LOS was 10 days (IQR, 6 to 17) for the SRT group and 10 days (IQR, 7 to 16) for the usual care group (median difference, 0 [95% CI, −1.5 to 3], P = .41) (**Table 2** and **Figure 2**). The estimated hazard ratio (SRT to usual care) was 1.11 (95% CI, 0.86 to 1.45). There were no differences between groups in the number of days taking a vasopressor, Confusion Assessment Method for the ICU-positive days, days receiving intravenous sedative drugs, days with restraint, or net ICU-related fluid balance (Table 2). Sensitivity analyses were performed for the primary outcome as described in the methods. The assumptions regarding the censored observations made little difference to the outcome, with a median 9 to 10 days in the SRT group and 10 days in the usual care group across the various scenarios. Hazard ratios ranged from 1.03 to 1.11 (with SRT patients more likely to get discharged) unadjusted for covariates and from 1.06 to 1.18 after adjusting for those covariates predictive of in-hospital death. The difference between groups was nonsignificant in each sensitivity analysis (P >.22).

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Table 1. Baseline Characteristics for Patients With Acute Respiratory Failure Receiving Standard Rehabilitation Therapy (SRT) vs Usual Care

	No. (%)		
	All (N = 300)	SRT (n = 150)	Usual Care (n = 150)
Age, mean (SD), y	56 (15)	55 (17)	58 (14)
Sex			
Women	166 (55.3)	84 (56.0)	82 (54.7)
Men	134 (44.7)	66 (44.0)	68 (45.3)
Race/ethnicity			
Hispanic or Latino	4 (1.3)	2 (1.3)	2 (1.3)
Black or African American	64 (21.3)	33 (22.0)	31 (20.7)
White	232 (77.3)	115 (76.7)	117 (78.0)
APACHE III score, mean (SD)[a]	76 (27)	76 (26)	75 (27)
Intensive care unit diagnosis			
Coma	5 (1.7)	1 (0.7)	4 (2.7)
Acute respiratory failure			
Without chronic lung disease	203 (67.7)	98 (65.3)	105 (70.0)
With chronic lung disease	92 (30.7)	51 (34.0)	41 (27.3)
Home oxygen	59 (19.7)	32 (21.3)	27 (18.0)
Dialysis prehospital	24 (8.0)	13 (8.7)	11 (7.3)
Mean arterial pressure, mean (SD), mm Hg	75.1 (22.4)	76.2 (22.3)	74.1 (22.5)
$Paco_2$, mean (SD), mm Hg	44.1 (17.2)	44.4 (18.2)	43.8 (16.2)
Pao_2 /Fio_2 ratio, mean (SD)	178.6 (83.8)	182.0 (81.2)	175.1 (86.4)
Noninvasive ventilation	21 (7.0)	11 (7.3)	10 (6.7)
Shock	69 (23.0)	36 (24.0)	33 (22.0)

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.

[a] APACHE III[19] score ranged from 0 to 299. A higher score indicates an increased risk of mortality.

Secondary Outcomes

Performance-based and self-reported measures of physical function are shown in **Table 3**. None of the scores were significantly different between groups at either ICU or hospital discharge. Strength values from handgrip and from handheld dynamometer did not differ between treatment groups at any of the measurement time points. The SPPB, SF-36 PFS, and FPI scores were not significantly different between groups at 2 or 4 months. However, each of these outcomes was significantly greater in the SRT group at the 6-month follow-up visit. At hospital discharge there was no difference in the proportion of SRT patients who could perform the 4-meter walk vs usual care (71% vs 61%, *P* = .15). By 6 months, those percentages had increased to 96% for the SRT group vs 88% for the usual care group (*P* = .037).

Health-related quality-of-life measures are shown in Table 3. SF-36 PHS, SF-36 MHS, and MMSE scores were not significantly different between groups at any time points.

The estimated intervention effects when analyses were repeated using multiple imputation assuming conservatively that all dropouts followed the pattern seen in the control group were decreased by approximately 40%. For example, the intervention effects at 6 months decreased from 1.06 to 0.60 for SPPB, 12.2 to 7.3 for SF-36 PFS, 0.21 to 0.12 for FPI, and 3.39 to 2.12 for SF-36 PHS. Only the SF-36 PFS effect remained significant (*P* = .04); the other *P* values were .11 for FPI, .16 for SPPB, and .19 for SF-36 PHS.

Outpatient physical therapy was not an intervention per treatment protocol; there was no difference in the number of patients (self-reported at each follow-up visit) who received outpatient or home physical therapy between hospital discharge and the 6-month follow-up visit (41 SRT patients vs 39 usual care patients, *P* = .69).

There were no differences in discharge destination between the SRT group and the usual care group (ie, home, long-term acute care, skilled nursing, or rehabilitation hospital) (eTable 1 in Supplement 2). Similarly, there were no differences between groups in post-index hospitalization readmissions or discharge emergency department visits without a hospital readmission. The percentage of each study group discharged from the hospital who were alive and hospital readmission–free at 6 months was 48.7% for the SRT group and 44.7% for the usual care group (*P* = .63). Post-hoc analyses indicated that the median number of ventilator-free days was 24 for both groups (median difference, 0 [95% CI, −2 to 1], *P* = .59), and the median number of ICU-free days was 19 for both groups (median difference, 0 [95% CI, −1.5 to 3], *P* = .83).

Missing Data

Death during the hospital stay was less than expected (12% observed vs 20% expected) as was death during the follow-up period (12% observed vs 15% expected). Dropout during the hospital stay was also less than expected (2% observed vs 5% expected). However, dropout during follow-up was greater than expected (24% observed from discharge to 6-month follow-up vs 10% expected). Neither dropout nor mortality differed between the study groups. Characteristics of those with and without missing data and those who did and did not drop out are shown in eTable 2 and eTable 3 in Supplement 2. Characteristics were fairly well balanced for those patients who re-

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Table 2. Outcomes for Standard Rehabilitation Therapy (SRT) vs Usual Care Among Patients With Acute Respiratory Failure

	Median (IQR)			
	SRT (n = 150)	Usual Care (n = 150)	Median Difference (95% CI)	*P* Value
Hospital days (primary outcome)	10.0 (6 to 17)	10.0 (7 to 16)	0 (−1.5 to 3)	.41[a]
Free days[b]				
Hospital	18 (7 to 22)	18 (9 to 21)	0 (−3 to 1.5)	.96[c]
Ventilator	24 (19 to 26)	24 (20 to 26)	0 (−2 to 1)	.59[c]
Intensive care unit				
Days	7.5 (4 to 14)	8.0 (4 to 13)	0 (−2.5 to 2)	.68[a]
Free days[b]	19 (8 to 23)	19 (12 to 24)	0 (−1.5 to 3)	.83[c]
Intravenous sedation[d]				
Days	2 (1 to 5)	2 (0 to 4)	0 (0 to 1.5)	.11
Days, %	30.8 (0.8 to 54.1)	27.1 (0 to 50.0)	3.8 (−5.5 to 14.5)	.14
Vasopressor				
Days	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	>.99
Days, %	0 (0 to 6.7)	0 (0 to 8.3)	0 (0 to 0)	.90
ICU fluid balance, cc	−68.5 (−806.6 to 664.4)	−148.8 (−766.8 to 520.2)	53.9 (−270.3 to 281.2)	.89
Restraint				
Days	1 (0 to 4)	1 (0 to 3)	0 (−1 to 1)	.71
Days, %	25.0 (0 to 55.8)	25.0 (0 to 50.0)	0 (−16.7 to 12.3)	.82
CAM-ICU[e]				
Negative				
Days	2 (0 to 3)	2 (0 to 4)	0 (−1 to 1)	.88
Days, %	24.5 (0 to 44.8)	20 (0 to 50.0)	3.4 (−5.0 to 10.1)	.91
Positive				
Days	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)	.77
Days, %	0 (0 to 12.5)	0 (0 to 9.1)	0 (0 to 0)	.71
RASS score of 4 or 5[f]				
Days	1 (0 to 4)	1 (0 to 3)	0 (−1 to 1)	.43
Days, %	14.6 (0 to 36.9)	14.3 (0 to 33.3)	1.8 (−6.7 to 10.5)	.71

Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit[20]; IQR, interquartile range; RASS, Richmond Agitation Sedation Scale.[21]

[a] Log-rank test.

[b] All free days are based on 28 days.

[c] Wilcoxon ranked sum.

[d] Intravenous sedation days were defined as any part of a day a continuous intravenous delivery occurred of fentanyl, morphine, midazolam, lorazepam, propofol or dexmedetomidine. Percentage of restraint days, CAM-ICU–positive days, CAM-ICU–negative days, and RASS score 4 or 5 days represent the percentage of ventilator days.

[e] CAM-ICU scores were positive or negative for delirium.

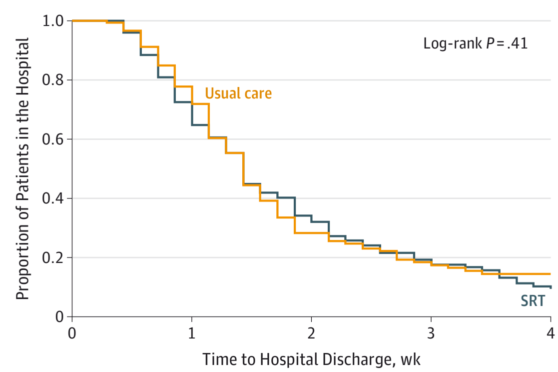
[f] RASS score ranged from −3 (moderate sedation) to 4 (combative).

mained in the study. Of the patients included in the follow-up analyses, APACHE III scores were lower (better) in the usual care group.

Adverse Events

There were no differences in adverse event reporting between study groups (eTable 4 in Supplement 2). The majority of adverse events captured were not specifically related to SRT delivery. Specific to SRT, there were no untoward events such as endotracheal tube removal, vascular access device removal, patient near-fall or fall, or cardiac arrest. However, there was an episode of asymptomatic bradycardia during a progressive resistance exercise session lasting less than 1 minute, with the patient completing the session afterwards.

Figure 2. Length of Stay for Patients With Acute Respiratory Failure Receiving SRT vs Usual Care



No. at risk					
SRT	150	102	44	22	10
Usual care	150	107	34	18	14

SRT indicates standardized rehabilitation therapy. Time zero indicates time of randomization.

Discussion

In this randomized, assessor-blinded study of SRT vs usual care for patients with acute respiratory failure, there was no difference in hospital LOS between groups. Similarly, SRT did not affect ventilator-free days or ICU-free days. Functional-related and health-related quality-of-life outcomes were similar for the 2 study groups at hospital discharge.

The amount of exercise delivered and performed while in-hospital was substantially different between SRT and usual care groups. The usual care group received physical therapy for only

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Table 3. Secondary Outcomes: Physical Function Measures and Health-Related Quality of Life for Patients With Acute Respiratory Failure, by Group

		ICU Discharge		Hospital Discharge		2-Month Follow-up		4-Month Follow-up		6-Month Follow-up	
Measurement	Group	Least Square Means (95% CI)	No. of Patients Providing Data	Least Square Means (95% CI)	No. of Patients Providing Data	Least Square Means (95% CI)	No. of Patients Providing Data	Least Square Means (95% CI)	No. of Patients Providing Data	Least Square Means (95% CI)	No. of Patients Providing Data
Physical Function											
Short Physical Performance Battery score[a]	SRT	1.6 (1.0 to 2.2)	86	4.7 (4.0 to 5.4)	106	8.7 (8.1 to 9.4)	88	8.9 (8.2 to 9.6)	88	9.0 (8.3 to 9.7)	84
	Usual care	1.9 (1.3 to 2.4)	98	4.7 (4.0 to 5.4)	98	7.8 (7.1 to 8.5)	76	8.0 (7.2 to 8.7)	79	8.0 (7.2 to 8.7)	81
	Difference	−0.3 (−1.1 to 0.5)		−0.01 (−1.0 to 0.9)		0.9 (−0.01 to 1.9)		1.0 (−0.03 to 1.9)		1.1 (0.04 to 2.1)	
	P Value[b]	.46		.97		.05		.06		.04	
Dynamometer strength, lb	SRT	20.3 (17.9 to 22.8)	67	23.7 (21.6 to 25.8)	100	28.5 (26.3 to 30.8)	84	28.8 (26.5 to 31.0)	85	31.1 (28.8 to 33.4)	78
	Usual care	22.8 (20.4 to 25.1)	77	23.9 (21.7 to 26.2)	86	28.0 (25.6 to 30.4)	73	29.6 (27.2 to 31.9)	75	30.8 (28.4 to 33.1)	77
	Difference	−2.4 (−5.8 to 1.0)		−0.2 (−3.3 to 2.9)		0.5 (−2.8 to 3.8)		−0.8 (−4.1 to 2.5)		0.4 (−2.9 to 3.7)	
	P Value[b]	.16		.90		.76		.63		.82	
Handgrip strength, kg	SRT	20.0 (17.8 to 22.3)	78	22.6 (20.6 to 24.6)	104	27.2 (25.1 to 29.2)	87	29.0 (26.8 to 31.2)	87	29.3 (26.9 to 31.6)	83
	Usual care	20.9 (18.7 to 23.1)	88	24.3 (22.2 to 26.4)	94	26.0 (23.8 to 28.1)	74	27.2 (24.9 to 29.4)	77	27.2 (24.8 to 29.6)	81
	Difference	−0.8 (−4.0 to 2.3)		−1.7 (−4.6 to 1.2)		1.2 (−1.8 to 4.2)		1.8 (−1.3 to 5.0)		2.0 (−1.3 to 5.4)	
	P Value[b]	.60		.25		.43		.25		.23	
SF-36 physical functioning scale score[c]	SRT			38.4 (33.2 to 43.7)	108	47.4 (41.8 to 53.1)	89	52.2 (46.7 to 57.7)	86	55.9 (50.0 to 61.7)	82
	Usual care			38.3 (32.8 to 43.8)	100	43.0 (37.0 to 49.0)	77	47.2 (41.4 to 53.0)	77	43.6 (37.5 to 49.7)	79
	Difference			0.1 (−7.6 to 7.8)		4.4 (−3.9 to 12.7)		5.0 (−3.0 to 13.0)		12.2 (3.8 to 20.7)	
	P Value[b]			.97		.29		.22		.001	
Functional Performance Inventory score[d]	SRT					2.0 (1.9 to 2.1)	89	2.2 (2.1 to 2.3)	86	2.2 (2.1 to 2.4)	83
	Usual care					2.0 (1.9 to 2.1)	75	2.1 (1.9 to 2.2)	77	2.0 (1.9 to 2.2)	79
	Difference					−0.03 (−0.2 to 0.1)		0.1 (−0.03 to 0.3)		0.2 (0.04 to 0.4)	
	P Value[b]					.74		.11		.02	
Health-Related Quality of Life											
SF-36 physical health summary score[e]	SRT			30.2 (28.4 to 32.1)	108	33.4 (31.4 to 35.5)	89	36.0 (33.8 to 38.2)	86	36.9 (34.6 to 39.3)	82
	Usual care			30.3 (28.4 to 32.2)	100	32.2 (31.0 to 34.4)	77	33.7 (31.4 to 36.0)	77	33.5 (31.1 to 36.0)	79
	Difference			−0.1 (−2.8 to 2.7)		1.2 (−1.8 to 4.3)		2.3 (−0.9 to 5.5)		3.4 (−0.02 to 7.0)	
	P Value[b]			.96		.43		.16		.05	
SF-36 mental health summary score[e]	SRT			43.6 (41.5 to 45.7)	108	46.3 (43.8 to 48.8)	89	47.8 (45.5 to 50.2)	86	48.8 (46.3 to 51.3)	82
	Usual care			43.3 (41.2 to 45.5)	100	46.2 (43.6 to 48.8)	77	47.7 (45.2 to 50.1)	77	46.4 (43.8 to 49.0)	79
	Difference			0.3 (−2.7 to 3.3)		0.1 (−3.5 to 3.7)		0.2 (−3.2 to 3.6)		2.4 (−1.2 to 6.0)	
	P Value[b]			.86		.96		.91		.19	
Mini-Mental State Examination score[c]	SRT			25.4 (24.7 to 26.1)	114	26.7 (25.9 to 27.5)	88	27.6 (27.0 to 28.2)	86	27.6 (27.0 to 28.2)	84
	Usual care			25.1 (24.3 to 25.8)	104	26.8 (26.0 to 27.7)	75	27.2 (26.5 to 27.8)	78	27.0 (26.4 to 27.6)	81
	Difference			0.3 (−0.7 to 1.3)		−0.1 (−1.3 to 1.1)		0.4 (−0.5 to 1.3)		0.6 (−0.2 to 1.4)	
	P Value[b]			.55		.86		.37		.17	

Abbreviations: ICU, intensive care unit; SRT, standardized rehabilitation therapy.

Metric conversion factor: To convert pounds to kilograms, divide by 0.45.

[a] Short Physical Performance Battery minimal clinically important difference is 1 unit.[13,22]

[b] Treatment effect at the given visit.

[c] SF-36 physical functioning scale and Mini-Mental State Examination were performed on hospital discharge and following appointments.

[d] Functional Performance Inventory was performed starting at first outpatient follow-up. Self-report mechanisms use higher scores to indicate greater levels of functioning.

[e] SF-36 mental and physical health summary minimal clinically important differences are 3 to 5 units.[15]

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12% of the study days and never received resistance training. In contrast, in the SRT group, passive range of motion occurred in 87% of study days, physical therapy in 55%, and progressive resistance exercise in 36%, with no significant hospital-based outcome differences observed. The volume of exercise delivered to SRT patients was delivered with 7 days per week availability. This structure may differ from the current practice in many US ICUs.[23] Others have also reported on the real-life delivery of ICU-related exercise being less than expected by ICU practitioners.[24-26] In view of these data, it is unclear what ICU exercise dose is required to affect outcomes by hospital discharge for patients with acute respiratory failure.

Following discharge, handgrip strength or strength measured by handheld dynamometer and health-related quality of life remained similar for the 2 groups. But from these exploratory analyses, the physical function measures (SPPB, SF-36 PFS, and FPI) were different at 6 months. The separation of the 2 groups' self-reported and objectively measured functional data over 6 months of follow-up contrasts with the lack of difference for hospital-centered outcomes.

These findings from the exploratory analyses may highlight the emerging role of placing long-term outcomes within critical care clinical trial design not only as a secondary outcome, but possibly as the primary outcome.[27-30] In view of the SPPB, SF-36 PFS, and FPI data at 6 months, the SRT group demonstrated a potential signal of improvement compared with the usual care group that was not evident at hospital discharge. It is not obvious what aspect of the SRT may have accounted for the differences at 6 months; however, both the physical therapy and the progressive resistance training emphasized lower extremity function. The exposure in the hospital may have inclined the SRT group to have greater movement while in the outpatient setting.

The findings from this study contrast with the outcomes of the study by Schweickert and colleagues,[7] which found greater improvements in activities of daily living at hospital discharge in an early ICU rehabilitation group than the control group, but no difference in hospital LOS either. The study by Walsh and colleagues[31] reported post-ICU hospital-based rehabilitation, including increased physical and nutritional therapy, did not improve physical recovery or quality-of-life scores at 3 months after enrollment. Outpatient-focused patient-level functional outcome differences were not detected in the study by Denehy and colleagues,[9] which linked an inpatient rehabilitation exercise repertoire with outpatient exercise instructions for a cohort of patients who were critically ill. Moss and colleagues[32] found that an intensive physical therapy program compared with a standard physical therapy program in which the intensive program continued for up to 28 days from randomization, including the outpatient setting, did not improve long-term physical functional performance at 6 months.

Study limitations include a higher than expected dropout (lost to follow-up and withdrawals, 24%) following hospital discharge. Also, there was no intervention following discharge; future study of ICU-initiated rehabilitation programs may need to include a bridge program of some outpatient exercise content to further optimize outcomes.[31,33]

Another potential limitation was that there was no explicit sedation protocol; the lack of a sedation protocol may have allowed patients in both groups to spend unnecessary days either unconscious or with a positive Confusion Assessment Method score.[34,35] Given that the intervention group had approximately 30% of ventilator days associated with intravenous continuous drip medications, and patients were unarousable on 15% of ventilator days, sedation may have been a barrier to receipt of early exercise. These data indicate the challenge of delivering a treatment modality requiring a conscious, engaged patient. Other modalities have been proposed such as functional electrical stimulation for the unconscious patient.[36] Additionally, multiple tests may have led to a spurious significant finding for the functional tests.

Conclusions

Among patients hospitalized with acute respiratory failure, SRT compared with usual care did not decrease hospital LOS.

ARTICLE INFORMATION

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Point Prevalence Study of Mobilization Practices for Acute Respiratory Failure Patients in the United States

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Objective: Early mobility in mechanically ventilated patients is safe, feasible, and may improve functional outcomes. We sought to determine the prevalence and character of mobility for ICU patients with acute respiratory failure in U.S. ICUs.

Design: Two-day cross-sectional point prevalence study.

Setting: Forty-two ICUs across 17 Acute Respiratory Distress Syndrome Network hospitals.

Patients: Adult patients (≥ 18 yr old) with acute respiratory failure requiring mechanical ventilation.

Interventions: We defined therapist-provided mobility as the proportion of patient-days with any physical or occupational therapy–provided mobility event. Hierarchical regression models were used to identify predictors of out-of-bed mobility.

Measurements and Main Results: Hospitals contributed 770 patient-days of data. Patients received mechanical ventilation on 73% of the patient-days mostly (n = 432; 56%) ventilated via an endotracheal tube. The prevalence of physical therapy/occupational therapy–provided mobility was 32% (247/770), with a significantly higher proportion of nonmechanically ventilated patients receiving physical therapy/occupational therapy (48% vs 26%; $p \le 0.001$). Patients on mechanical ventilation achieved out-of-bed mobility on 16% (n = 90) of the total patient-days. Physical therapy/occupational therapy involvement in mobility events was strongly associated with progression to out-of-bed mobility (odds ratio, 29.1; CI, 15.1–56.3; $p \le 0.001$). Presence of an endotracheal tube and delirium were negatively associated with out-of-bed mobility.

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Conclusions: In a cohort of hospitals caring for acute respiratory failure patients, physical therapy/occupational therapy–provided mobility was infrequent. Physical therapy/occupational therapy involvement in mobility was strongly predictive of achieving greater mobility levels in patients with respiratory failure. Mechanical ventilation via an endotracheal tube and delirium are important predictors of mobility progression. (*Crit Care Med* 2016; XX:00–00)

Key Words: early mobility; intensive care unit acquired weakness; intensive care unit rehabilitation

Acute respiratory failure survivors experience long-term morbidity after critical illness (1–3). Physical functional impairments reduce overall health-related quality of life for survivors increasing healthcare utilization and unemployment (1, 4, 5). Early physical and occupational therapy (PT/OT) for respiratory failure patients improves functional outcomes at hospital discharge (6–10).

PT/OT utilization in the ICU remains low. One-day point prevalence studies in Germany and Australia/New Zealand report most patients on mechanical ventilation (MV) do not receive out-of-bed mobility in the ICU. Across 116 German hospitals, ICU administrators reported only 8% of ventilated patients received out-of-bed mobility (11) and across 38 Australian/New Zealand ICUs, only 3% achieved sitting at the edge of the bed with none standing, transferring to chair or walking (12).

Across the United States, the prevalence of ICU mobility, as part of routine clinical care, remains unknown. As the literature supporting mobility expands, estimates of current clinical practice are necessary to inform implementation efforts. Our aim was to report the prevalence of PT/OT-provided mobility in respiratory failure patients, define the type and frequency of ICU mobility and identify factors associated with mobility progression.

METHODS

We performed a 2-day cross-sectional point prevalence study across acute respiratory distress syndrome (ARDS) Network (ARDSNet) hospitals. Hospitals were invited to participate in the two study dates, 3 weeks apart (Wednesday, January 15, 2014, and Tuesday, February 4, 2014); participation was voluntary. Each ARDSNet site contributed data from at least one hospital. In total, 17 (39%) of 44 hospitals participated, with two hospitals completing estimates outside of the prespecified study dates. Each site obtained institutional review board approval with waiver of consent for the observational study.

Patient Selection

We included adult (≥ 18 yr old) patients diagnosed with acute respiratory failure (requiring > 48 hr of MV) at any point during their ICU stay physically located in the ICU at noon. MV was defined as any ventilation via an endotracheal tube (ETT), tracheostomy tube, or noninvasive positive pressure ventilation. Since we aimed to capture any patient who would have met criteria for early mobility in earlier trials (9), ongoing MV use was not required for eligibility.

Mobility Events

A therapist-provided mobility event was defined as receipt of at least one PT/OT-provided event on a study day. Mobility events not performed by a therapist were also recorded such that we ascertained any mobility event performed on a patient with respiratory failure on either study date. Events were reported by PT/OT and/or nursing using bedside real-time event recording on custom-made case report forms. Events were subsequently confirmed verbally between study coordinators and the bedside nurse and categorized using a published hierarchical ICU mobility scale (13). Standardized forms allowed for free text of any activities performed outside of the standardized mobility scale. Study coordinators received training on the activity case report forms prior to the study date. Mobility events performed by multiple providers (e.g., PT/OT and bedside nursing) were reported on a single form. Out-of-bed mobility was defined as sitting at the edge of the bed, standing, standing and moving to chair, marching in place, or walking. Adverse outcomes that occurred during a mobility session were coded using international consensus adverse outcome guidelines (14).

Patient Demographics/Clinical Characteristics

Trained abstractors abstracted physiologic data from the medical record with values reported as that closest to 8 AM on the study date. Study coordinators interviewed bedside nurses to obtain reasons mobility did not occur and invasive catheter data. Potential medical exclusions were defined using published ICU mobility safety guidelines (15).

ICU Characteristics

Administrators for participating ICUs were contacted after study completion to participate in a survey regarding ICU characteristics. Medical directors ($n = 25$) and nurse managers ($n = 15$) participated with at least one hospital administrator from each of the 17 hospitals contributing data.

Statistical Analysis

The prevalence of therapist-provided mobility was estimated as the proportion of patient-days with any therapist-provided mobility event during the two study days. Patients contributing data to both study dates were included in the prevalence estimates and logistic regression models the large time interval between events. Hierarchical multivariable logistic regression models with random effects for ICU site were used to evaluate predictors of therapist-provided therapy and out-of-bed mobility. Predictors of interest based on steering committee expert consensus included: MV, vasoactive agent use, coma (Richmond Agitation Sedation Score [RASS] of –4 or –5), agitation (RASS, ≥ 2), intravascular catheter location, sedative infusion use, weight, and delirium (Confusion Assessment Method-ICU [CAM-ICU] positive/negative). Missing CAM-ICU status was categorized as CAM-ICU unable to assess and included as a unique category. All statistical analyses were completed using SAS software (SAS Corporation, Cary, NC).

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RESULTS

ICU Characteristics

A total of 42 ICUs from 17 hospitals participated. Most ICUs were medical (51%), trauma (12%), or mixed medical/surgical (9%) ICUs. ICUs averaged 23 beds in the unit (SD, 7) with six ICUs (SD, 3) in the hospital. Most hospitals reported physician-initiated mobility (73%) and more than half (53%) reported use of a mobility protocol.

Patient Baseline Characteristics

A total of 744 unique patients contributed 770 patient-days of data after exclusion of 17 patients (2.1%) who were ineligible due to ICU discharge prior to noon (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C222; **legend**, Supplemental Digital Content 3, http://links.lww.com/CCM/C224). Twenty-six patients (4%) were in the ICU on both study dates. Patients were mostly middle aged (mean age, 56 yr; SD, 16), men (60%), and most were ambulatory (80%) and independent with activities of daily living (78%) prior to admission. Most (62%) received care in a medical ICU (**Table 1**).

Study Day Characteristics

Patients received MV, via an ETT (ETT: n = 432, 56%; tracheostomy: n = 81, 10%) or noninvasively (n = 47, 6%) on 72% (n = 566) of the patient-days with a mean F_{IO_2} of 0.43 (SD, 0.14) and positive end-expiratory pressure (PEEP) of 7 (SD, 3) cm H_2O. On 6% (n = 48) of the patient-days, patients were receiving more than 60% F_{IO_2}, and on 7% (n = 56) of the patient-days, they received more than 10 cm H_2O of PEEP. Patients received more than 60% F_{IO_2} and more than 10 PEEP on 3% (n = 21) of the patient-days. Patients were on an infusion of a vasoactive medications on 21% of the (n = 174) patient-days and received hemodialysis on 15%

TABLE 1. Patient Characteristics Stratified by Presence of Mechanical Ventilation

	All (n = 770)	Mechanical Ventilation (n = 559)[a]	No Mechanical Ventilation (n = 211)[a]	p
Age, mean ± SD[b]	56 ± 16	56 ± 16	57 ± 16	0.69
Male, n (%)	465 (60)	330 (59)	135 (64)	0.24
ICU category[c]				
Medical	477 (62)	374 (67)	103 (49)	< 0.001
Surgical	238 (31)	158 (28)	80 (38)	
Neurologic	55 (7)	27 (5)	28 (13)	
Reason for admission[d]				
ARDS	140 (18)	117 (21)	23 (11)	0.002
Chronic obstructive pulmonary disease exacerbation	33 (4)	23 (4)	10 (5)	0.86
Sepsis from lung source	96 (13)	88 (16)	8 (4)	< 0.001
Sepsis from other source	103 (13)	79 (14)	24 (11)	0.38
Hemorrhage	39 (5)	23 (4)	16 (8)	0.08
Trauma	59 (8)	37 (7)	22 (10)	0.11
Malignancy	18 (2)	10 (2)	8 (4)	0.17
ARDS diagnosis during hospitalization	279 (36)	237 (43)	42 (20)	< 0.001
Ambulatory at baseline	533 (80)	379 (80)	154 (82)	0.46
Independent with activities of daily living at baseline	505 (78)	359 (78)	146 (80)	0.55
Mode of ventilation[e], n (%)				
Endotracheal tube	432 (56)	432 (77)	NA[e]	
Tracheostomy tube	81 (11)	81 (15)	NA	
Noninvasive positive pressure	46 (6)	46 (8)	NA	
Ventilation (noninvasive positive pressure ventilation)				
F_{IO_2}, mean ± SD		0.43 ± 0.14	NA	
Positive end-expiratory pressure (cm H_2O), mean ± SD		7 ± 3	NA	

(*Continued*)

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TABLE 1. (*Continued*). Patient Characteristics Stratified by Presence of Mechanical Ventilation

	All (n = 770)	Mechanical Ventilation (n = 559)[a]	No Mechanical Ventilation (n = 211)[a]	p
Vasoactive infusions[d], n (%)				
Vasopressors	159 (21)	149 (27)	10 (5)	< 0.001
Inotropes	15 (2)	12 (2)	3 (1)	0.72
Neither	606 (79)	408 (73)	198 (94)	< 0.001
Body mass index, n (%)				
≤ 18.5	32 (5)	22 (5)	10 (6)	0.82
18.5–25	156 (25)	113 (25)	43 (25)	
25–30	174 (28)	124 (27)	50 (29)	
> 30	264 (42)	197 (43)	67 (39)	
Weight (kg), mean ± SD	89 ± 31	90 ± 33	87 ± 26	0.10
Hemodialysis, n (%)	112 (15)	96 (18)	16 (8)	0.001
Type of hemodialysis, n (%)				
Continuous	63 (8)	55 (10)	8 (4)	0.003
Intermittent	49 (7)	41 (8)	8 (4)	
RASS, median (IQR)	0 (−2 to 0)	−1 (−3 to 0)	0 (−1 to 0)	< 0.001
Agitation (RASS ≥ +2)[f], n (%)	31 (4)	28 (5)	3 (1)	0.06
Delirium, n (%)				
Coma (RASS −4 or −5)	94 (12)	84 (15)	10 (5)	< 0.001
Delirium (CAM-ICU positive)	113 (15)	89 (16)	24 (11)	
No delirium (CAM-ICU negative)	219 (28)	139 (25)	80 (38)	
No category	344 (45)	247 (44)	97 (46)	
Sedative/analgesia infusions, n (%)				
Benzodiazepines	65 (8)	64 (11)	1 (0.5)	< 0.001
Dexmedetomidine	63 (8)	49 (9)	14 (7)	0.42
Propofol	162 (21)	158 (28)	4 (2)	< 0.001
Opioids	215 (28)	200 (36)	15 (7)	< 0.001
None	430 (56)	251 (45)	179 (85)	< 0.001
Sedative/analgesia boluses, n (%)				
Benzodiazepines	116 (15)	105 (19)	11 (5)	< 0.001
Opioids	288 (37)	215 (39)	73 (35)	0.37
None	456 (59)	320 (57)	136 (65)	0.08
CAM-ICU score, n (%)				
Negative	221 (46)	141 (39)	80 (68)	< 0.001
Positive	116 (24)	92 (26)	24 (21)	
Unable to perform	140 (29)	127 (35)	13 (11)	
Antipsychotic use, n (%)	119 (16)	94 (17)	25 (12)	0.12

(*Continued*)

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TABLE 1. (*Continued*). Patient Characteristics Stratified by Presence of Mechanical Ventilation

	All (*n* = 770)	Mechanical Ventilation (*n* = 559)[a]	No Mechanical Ventilation (*n* = 211)[a]	*p*
Intravascular catheters, *n* (%)				
Central venous catheter				< 0.001
Femoral	32 (4)	28 (5)	4 (2)	
All other sites	451 (60)	349 (65)	102 (49)	
None	263 (35)	162 (30)	101 (49)	
Hemodialysis				
Femoral	19 (2)	17 (3)	2 (1)	0.87
All other sites	92 (12)	78 (14)	14 (7)	
None	659 (86)	464 (83)	195 (92)	
Arterial				< 0.001
Femoral	36 (5)	31 (6)	5 (2)	
All other sites	267 (35)	214 (39)	53 (26)	
None	451 (60)	302 (55)	149 (72)	
Chest tube	107 (14)	76 (14)	31 (15)	0.81
Intraaortic balloon pump	4 (0.5)	4 (0.7)	0 (0)	0.50
Left ventricular assist device	8 (1)	5 (0.9)	3 (1)	0.82
Foley catheter	606 (80)	470 (86)	136 (66)	< 0.001
Rectal tube	134 (18)	111 (20)	23 (11)	0.005
Potential contraindication to mobility[g]	112 (15)	99 (18)	13 (6)	< 0.001

ARDS = acute respiratory distress syndrome, CAM-ICU = Confusion Assessment Method-ICU, IQR = interquartile range, NA = not applicable, RASS = Richmond Agitation Sedation Scale.

[a]Missing data: acute respiratory distress syndrome diagnosis (*n* = 3 of mechanically ventilated patients, 0.4%), ambulation status (*n* = 24 of nonmechanically ventilated, 112 of mechanically ventilated, 18%), activity of daily living (*n* = 29 of nonmechanically ventilated, 97 of mechanically ventilated, 16%). FIO_2 *n* = 14 (2.5%), positive end-expiratory pressure *n* = 31 (5.5%), body mass index *n* = 144 (18.7%), weight *n* = 55 (7.1%), hemodialysis *n* = 22 (2.9%), Richmond Agitation Sedation Scale (RASS) *n* = 130 (16.9%), Confusion Assessment Method-ICU *n* = 293 (38.1%), antipsychotics *n* = 10 (1.3%), central venous catheter *n* = 24 (3.1%), arterial line *n* = 16 (2%), chest tube *n* = 19 (2.4%), intraaortic balloon pump *n* = 19 (2.4%), left ventricular assist device *n* = 19 (2.4%), Foley *n* = 16 (2%), rectal tube *n* = 16 (2%).

[b]Age > 90 coded as 90 for calculation (*n* = 2 of mechanically ventilated, 0.3% of total cohort).

[c]ICU types categorized as medical include: medical *n* = 389 (51%), medical/cardiac *n* = 2 (0.3%), cardiac *n* = 15 (2%), medical/surgical *n* = 71 (9%) ICU types categorized as surgical: surgical *n* = 69 (9%), cardiac surgery *n* = 29 (4%), burns *n* = 19 (3%), trauma *n* = 91 (12%), cardiothoracic *n* = 28 (4%), pediatric *n* = 2 (0.3%), ICU types categorized as neurologic include: neurologic *n* = 55 (7%).

[d]Categories are not mutually exclusive.

[e]High frequency oscillatory ventilation use, *n* = 1 (0.1%), extracorporeal membrane oxygenation use, *n* = 8 (1%).

[f]Categorized as RASS ≥ +2, RASS < +2, no RASS reported.

[g]Contraindications defined per previously published mobility safety recommendations: Hodgson et al (15).

(*n* = 112) of the patient-days (63 [8%] continuous, 49 [7%] intermittent). Sedative infusions were used on 37% of the patient-days (*n* = 294) with most patients receiving propofol infusion (propofol: 21%, *n* = 163; benzodiazepines: 9%, *n* = 68; dexmedetomidine: 8%, *n* = 63). The median RASS score was 0 (interquartile range [IQR], –2 to 0), with 15% (*n* = 97) of patient-days spent in a "coma" (i.e., RASS –4 or –5). Median RASS scores differed significantly between mechanically (median, –1; IQR, –3 to 0) and nonmechanically ventilated (median, 0; IQR, –1 to 0) patients ($p < 0.001$). Delirium was present on 22% (*n* = 113) of the patient-days although 281 patient-days (36%) had no CAM-ICU assessment documented (**Table 2**). A potential safety exclusion was documented on 15% of the patient-days (*n* = 112) and more frequently reported in mechanically ventilated patients (18% mechanically ventilated vs 6% nonmechanically ventilated; $p \leq 0.001$). The most commonly reported exclusions were medical instability (21%), coma (12%), and weakness (11%) (**Fig. 1**).

Therapist-Provided Mobility

Patients were treated by PT/OT on 247 patient-days for an overall prevalence of therapist-provided ICU mobility of 32% (247/770). Nonmechanically ventilated patients were significantly more likely to receive PT/OT than mechanically ventilated patients (48% vs 26%; $p < 0.001$).

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TABLE 2. Predictors of Out-of-Bed Mobility for Patients Ventilated Via an Endotracheal Tube

Clinical Predictor	All ($n = 432$)	Out-of-Bed Mobility ($n = 45$)	In-Bed Mobility ($n = 387$)	p
Vasoactive agent (vasopressor and/or inotrope), n (%)	140 (32)	8 (18)	132 (34)	0.04
Benzodiazepine or propofol infusion, n (%)	191 (44)	15 (33)	176 (46)	0.16
Bolus benzodiazepine use, n (%)	86 (20)	4 (9)	82 (21)	0.08
Opioid infusion, n (%)	173 (40)	17 (38)	156 (40)	0.87
Bolus opioid use, n (%)	176 (41)	15 (33)	161 (42)	0.37
Intravascular catheter (no catheter referent), n (%)				
Internal jugular, femoral, subclavian, or radial catheter	316 (73)	27 (60)	289 (75)	0.04
Unknown	7 (2)	0 (0)	7 (2)	
Delirium assessment (no delirium CAM-ICU negative referent), n (%)				
Delirium (CAM-ICU positive)	73 (17)	7 (16)	66 (17)	0.05
Unable to assess (CAM-unable)	114 (26)	5 (11)	109 (28)	
Delirium status unknown (CAM-missing)	148 (34)	18 (40)	130 (34)	
Agitation assessment (no agitation RASS < 2 referent), n (%)				
Agitation (RASS ≥ 2)	21 (5)	0 (0)	21 (5)	0.001
Agitation status unknown (RASS missing)	49 (11)	12 (27)	37 (10)	
Physical or occupational therapy involvement, n (%)	88 (20)	38 (84)	50 (13)	< 0.001
ICU type (medical ICU referent), n (%)				
Neurologic ICU	22 (5)	3 (7)	19 (5)	0.57
Surgical ICU	121 (28)	15 (33)	106 (27)	
Ambulatory prior to admission (not ambulatory referent), n (%)				
Ambulatory	310 (72)	35 (78)	275 (71)	0.33
Unknown	60 (14)	3 (7)	57 (15)	
Age (yr), mean (SD)	56 (16)	59 (15)	55 (16)	0.11
Weight (kg), mean (SD)	90 (31)	78 (24)	92 (32)	0.001

CAM-ICU = Confusion Assessment Method-ICU, RASS = Richmond Agitation Sedation Scale.

All Mobility Events

Patients received mobility events from any provider type on 65% ($n = 501$) of the total 770 patient-days. Most events were provided by nursing (68%) with most activity sessions involving one provider (44%). Two care providers were involved in 15% ($n = 118$) of sessions, whereas few sessions ($n = 47$; 6%) involved more than two providers. Providers involved in activity sessions included: physical, occupational, respiratory and speech therapists or technicians, nurses, physicians, hospital assistants, advanced care providers, and patient family.

Activity delivered in the absence of PT/OT was of lower intensity ($p < 0.001$ compared with PT/OT-delivered activity) with 21% ($n = 43/247$) of patients achieving out-of-bed mobility without PT/OT involvement. Most mobility events for patients on MV (208/336; 62%) consisted of passive activities (range of motion or passively moved to chair). Mechanically ventilated patients usually participated in a single session/day (median, 1; IQR, 0–2). Nonmechanically ventilated patients received mobility on 80% ($n = 168$) of the patient-days, with a median one session per day (IQR, 1–2). Significantly more mobility sessions occurred in nonmechanically versus mechanically ventilated patients ($p < 0.001$).

Out-of-Bed Mobility in Patients on MV

Mechanically ventilated patients achieved out-of-bed mobility on 16% ($n = 90$) of the patient-days progressing to sitting at the edge of the bed on 6% ($n = 31$), standing on 2% ($n = 13$), transferring to chair from standing on 3% ($n = 18$), marching in place on 1% ($n = 5$), and walking on 4% ($n = 23$) of patient-days (**Fig. 2**). Nonmechanically ventilated patients were significantly more likely than mechanically ventilated patients to achieve out-of-bed mobility (56% vs 16%; $p < 0.001$) (**Fig. S2,** Supplemental Digital Content 2, http://links.lww.com/CCM/C223; legend, Supplemental Digital Content 3, http://links.lww.com/CCM/C224).

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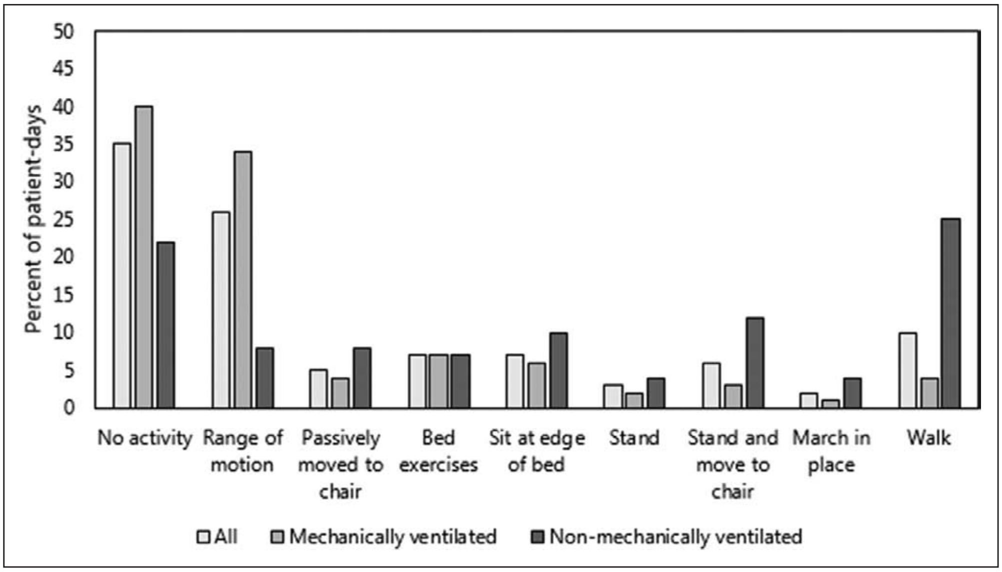

Figure 1. Reasons for no reported mobility. Presence of coma and medical instability were the most commonly reported reasons for lack of ICU mobility.

Adverse Events

Seven potential safety events occurred in 807 mobility events (0.9%). Potential safety events included new arrhythmias (n = 3), oxygen desaturations (< 85% for > 3 min; n = 2), hypotension (mean arterial pressure, < 55 mm Hg for > 3 min; n = 1) and an endotracheal dislodgement (n = 1). Six (86%) of these events occurred in patients receiving lower level mobility, with four events occurring during range of motion and two during passive chair transfer. The single ETT dislodgement occurred during an in-bed passive range of motion session.

Predictors of ICU Mobility

PT/OT involvement was strongly associated with progression to out-of-bed mobility (**Table 3**; adjusted odds ratio [OR], 26.1; 95% CI, 14.2–47.9; p < 0.001). Use of MV via an endotracheal or tracheostomy tube was negatively associated with achieving out-of-bed mobility (ETT: adjusted OR, 0.10, 95% CI, 0.05–0.20; tracheostomy tube: adjusted OR, 0.20, 95% CI, 0.09–0.47; p < 0.001) as was presence of delirium (adjusted OR, 0.41; 95% CI, 0.18–0.93; p = 0.003). Although weight was significantly associated with out-of-bed mobility in bivariate analysis (mean weight 78 kg in patients achieving out-of-bed mobility vs 92 kg receiving only in-bed mobility, p = 0.001), it was not independently associated in the adjusted model (OR, 0.99; 95% CI, 0.98–1.00).

Among patients receiving MV via an ETT, PT/OT involvement remained highly associated with out-of-bed mobility (**Table 4**; adjusted OR, 138.4; 95% CI, 29.8–643.5; p < 0.001). Presence of delirium or coma remained negatively associated with out-of-bed mobility (delirium present: adjusted OR, 0.13, 95% CI, 0.02–0.75; coma adjusted: OR, 0.05, 95% CI, 0.01–0.40; p = 0.02).

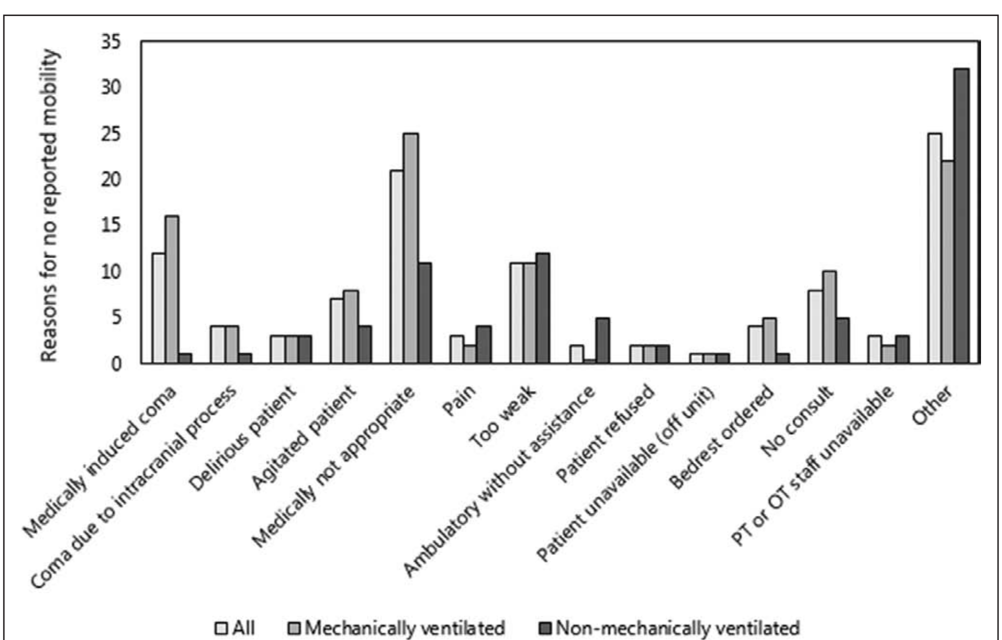

Figure 2. Highest level of mobility achieved by patients on the study dates. Patients on mechanical ventilation were significantly less likely to achieve out-of-bed mobility compared with patients off mechanical ventilation (p < 0.001). Reported categories are mutually exclusive. OT = occupational therapy, PT = physical therapy.

Hospital-Level Variance

There was significant variation in clinical practice between participating hospitals. PT/OT participation in mobility varied with a minimum participation of 7% (n = 3/45) to a maximum of 74% (n = 31/42) in some study hospitals (p = 0.03). Achievement of out-of-bed mobility for mechanically ventilated patients varied between 4% (n = 2/45) and 67% (n = 26/39) between study hospitals (p = 0.04). Significant between-hospital differences remained after adjustment for patient demographics with between-hospital differences accounting for 66% (SE, 0.31) of the overall model variance.

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TABLE 3. Hierarchical Multivariable Logistic Regression Model of Factors Associated With Out-of-Bed Mobility[a]

Clinical Predictor	OR	95% CI	*p*
Age (yr)	1.02	1.00–1.03	0.07
ICU type (medical ICU referent)			
Neurologic ICU	0.45	0.14–1.44	0.11
Surgical ICU	1.50	0.72–3.09	
Ambulatory prior to admission (not ambulatory referent)			
Ambulatory	1.58	0.75–3.34	0.20
Unknown	0.80	0.29–2.18	
Route of MV (no MV referent)			
Endotracheal tube	0.10	0.05–0.20	< 0.001
Tracheostomy tube	0.21	0.08–0.52	
Noninvasive positive pressure ventilation	0.56	0.19–1.74	
Vasoactive agent (vasopressor and/or inotrope)	0.59	0.23–1.49	0.24
Weight (kg)[b]	0.99	0.98–1.00	0.02
Agitation assessment (no agitation RASS < 2 referent)			
Agitation (RASS ≥ 2)	0.15	0.01–1.87	0.06
Agitation status unknown (RASS missing)	2.13	0.92–4.90	
Bolus opioid use	0.84	0.43–1.62	0.57
Bolus benzodiazepine use	0.73	0.28–1.91	0.49
Delirium assessment (no delirium CAM-ICU negative referent)			
Delirium (CAM-ICU positive)	0.37	0.15–0.89	
Unable to assess (CAM-unable)	0.15	0.05–0.44	
Delirium status unknown (CAM-missing)	0.35	0.17–0.74	0.003
Intravascular catheter (no catheter referent)			
Internal jugular, femoral, subclavian, or radial catheter	0.58	0.31–1.07	0.07
Unknown	0.17	0.02–1.34	
Physical therapy or occupational therapy involvement	29.1	15.1–56.3	< 0.001

CAM-ICU = Confusion Assessment Method-ICU, MV = mechanical ventilation, OR = odds ratio, RASS = Richmond Agitation Sedation Scale.
[a]Out-of-bed mobility: sitting at the edge of the bed, standing, marching in place, and walking.
[b]Missing weight data ($n = 55$ patients, 715/770 patients included in final model).

DISCUSSION

These data represent the first U.S. estimates of mobility in routine clinical practice for respiratory failure patients. Patients with respiratory failure received therapist-provided mobility on 32% of patient-days. Out-of-bed mobility was delivered on a minority of patient-days to mechanically ventilated patients (16%), with patients rarely progressing to walking (4% of patient-days). PT/OT involvement was strongly associated with mobility progression, whereas MV via an ETT and delirium were negatively associated.

Our prevalence estimates of ICU mobility are similar to prior estimates from Germany and Australia/New Zealand (11, 12). Unlike the prior studies, we included two prevalence dates on different weekdays to account for daily variation in rehabilitation care to better estimate prevalence. Additionally, we captured actual rather than reported mobility. Despite reducing the chance of misclassification with two separate study dates, our estimates remained low. Our estimates were comparable to those reported in Germany where only 24% of mechanically ventilated patients received mobility with 8% mobilizing out of bed (11) and Australia/New Zealand where no (0/391) patients on MV sat out of bed, stood or ambulated (12).

The low levels of mobility observed highlight discrepancies between reported and actual delivery in clinical practice. Survey of ICU administrators across Michigan reported ICU mobility use in 39% of their mechanically ventilated patients

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TABLE 4. Hierarchical Multivariable Logistic Regression Model of Factors Associated With Out-of-Bed Mobility Restricted to Patients on Mechanical Ventilation Via an Endotracheal Tube[a]

Clinical Predictor	OR	95% CI	*p*
Age (yr)	1.05	1.01–1.09	0.02
ICU type (medical ICU referent)			
Surgical ICU	3.96	0.90–17.38	0.15
Neurologic ICU	0.74	0.08–6.93	
Ambulatory prior to admission (not ambulatory referent)			
Ambulatory	2.44	0.52–11.68	0.41
Unknown	1.03	0.11–9.62	
Vasoactive agent (vasopressor and/or inotrope)	0.59	0.16–2.19	0.43
Weight (kg)[b]	0.97	0.95–1.00	0.02
Delirium assessment (no delirium CAM-ICU negative referent)			
Delirium (CAM-ICU positive)	0.13	0.02–0.75	0.02
Unable to assess (CAM-unable)	0.05	0.01–0.40	
Delirium status unknown (CAM-missing)	0.21	0.04–1.09	
Benzodiazepine or propofol infusion	1.43	0.39–5.25	0.59
Bolus benzodiazepine use	0.40	0.08–1.98	0.26
Opioid infusion	2.01	0.58–7.03	0.27
Bolus opioid use	0.37	0.10–1.39	0.14
Physical therapy or occupational therapy involvement	138.4	29.75–643.49	< 0.001

CAM-ICU = Confusion Assessment Method-ICU, OR = odds ratio.
[a]Out-of-bed mobility: sitting at the edge of the bed, standing, marching in place, and walking.
[b]Missing weight data ($n = 29$ patients, 403/432 patients included in final model).

with 10% achieving ambulatory status upon ICU discharge (16). Similarly, survey of nurse managers across Washington state reported 47% of mechanically ventilated patients received out-of-bed mobility (17). Our results suggest that reported and actual delivery of mobility may differ substantially and further studies are needed to understand reasons for this discordance.

Presence of PT/OT involvement was strongly associated with mobility in our cohort. Quality improvement studies suggest dedicated ICU therapists enhance access to mobility (11, 18–20). Stepwise progression through a therapy-driven ICU mobility protocol resulted in increased mobility uptake with length of stay and mortality reductions in a cohort of respiratory failure patients (7, 8). Randomized early involvement of PT/OT for mechanically ventilated patients improved functional independence at discharge (9, 21). Our findings support earlier evidence suggesting therapist involvement may increase mobility progression.

Although PT/OT involvement was strongly associated with out-of-bed activity, it was not required. Nursing providers provided most of the activity events in our cohort either alone or in conjunction with PT/OT and patients achieved out-of-bed mobility in the absence of PT/OT on 21% of patient-days. Nursing staff may represent an expandable workforce for ICU mobility delivery; however, little is known regarding their potential role in optimal mobility delivery. Similarly, it is not known if the most common activities provided by nurses—passive movement in and out of bed—should be considered as part of "ICU mobility" at all. Furthermore, the large PT/OT association may reflect institutional commitment to mobility rather than staffing. If PT/OT involvement is a surrogate marker of institutional mobility commitment, then increasing PT/OT staffing alone may be insufficient to increase mobility intensity. This disconnect between culture and staffing may explain why prevalence across countries remains low (11, 12) despite institution of high-intensity staffing models. Qualitative studies indicate that factors beyond staff including degree of buy-in, perceived workload, and rehabilitation training are important for implementation and sustainability of an ICU rehab program (22). Studies are needed to better understand the influence of these organizational factors in ICU mobility uptake.

MV via an ETT and delirium were important negative predictors of out-of-bed mobility in our study. Our results support prior notions that MV via an ETT is an important barrier to ICU mobility despite multiple safety studies. Studies report adverse event rates of less than 1% in respiratory failure patients (6, 14, 23). Our adverse event rate was 0.9%; most of the events were minor. The single ETT dislodgment occurred in a patient

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receiving passive range of motion. Yet, intubation remains a frequently reported reason for mobility avoidance. Data are needed regarding methods for overcoming potential barriers between perceived and actual safety of mobility in intubated patients.

Delirium in critically ill patients represents an increasingly recognized predictor of worse outcomes after critical illness (24). Despite this, many patients in our cohort received no CAM-ICU delirium screening on our study dates. This lack of routine CAM-ICU administration is not unique to our cohort. Across Michigan ICUs, only 31% of ICUs performed routine delirium assessments for mechanically ventilated patients (16). Report of delirium assessment as part of standard practice was predictive of report of higher level activity (OR, 15.6 vs 4.5; $p = 0.006$ delirium vs no delirium assessment) in the Michigan cohort (16). Similarly, in our cohort, patients who underwent screening were frequently delirious, and delirium was predictive of failure to achieve higher mobility levels. While early mobility is associated with reductions in delirium duration (9), there is little data guiding mobilization practices specifically in delirious patients.

Predictably, we found significant between-hospital variation around mobility utilization. Studies identify site as a significant predictor of ICU mobility (23, 25). Between-hospital variation explained 66% of our overall cohort variance after adjustment for patient factors. Hospitals that provided out-of-bed mobility often did so in patients with greater severity of illness or organ dysfunction. This suggests that local care practices exert substantial effects on the overall uptake of ICU mobility. A number of studies support the need for broad multidisciplinary, ICU culture change for acceptance of ICU mobility (9, 22, 26, 27). Utilization of high-performing hospitals as a care model for ICU mobility delivery may serve to increase access broadly while use of ICU mobility quality initiatives may enhance local uptake.

There are several potential limitations to our study. First, mobility assessments were unblinded potentially leading to greater mobility delivery. Efforts were made to limit knowledge of the study and the relatively low observed prevalence makes it unlikely that single day escalation of mobility efforts biased the overall estimates. Second, participation was voluntary and limited to ARDSNet hospitals reflecting sites with larger clinical and research infrastructure and/or targeted interest in mobility potentially limiting the generalizability of our results. Third, restriction of study dates to weekdays rather than weekends may lead to overestimation of ICU activity as activities generally occur less frequently on weekends. Finally, despite our attempts to exclude patients with potential contraindications to mobility, we were unable to reliably exclude them due to inconsistent charting. Contraindications varied throughout the study date, changing mobility eligibility over time, and potential contraindications conflicted across centers depending on institutional mobility comfort level. It is possible that our estimates underestimate the true prevalence of ICU mobility in medically eligible patients.

CONCLUSIONS

In a cohort of hospitals caring for acute respiratory failure patients, PT/OT-provided mobility occurred infrequently. PT/OT involvement in ICU mobility was strongly predictive of out-of-bed mobility for patients on MV. MV via an ETT and presence of delirium were negatively associated with out-of-bed mobility. There was significant variability around ICU mobility delivery between hospitals.

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Adapting the ABCDEF Bundle to Meet the Needs of Patients Requiring Prolonged Mechanical Ventilation in the Long-Term Acute Care Hospital Setting: Historical Perspectives and Practical Implications

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Abstract

When robust clinical trials are lacking, clinicians are often forced to extrapolate safe and effective evidence-based interventions from one patient care setting to another. This article is about such an extrapolation from the intensive care unit (ICU) to the long-term acute care hospital (LTACH) setting. Chronic critical illness is an emerging, disabling, costly, and yet relatively silent epidemic that is central to both of these settings. The number of chronically critically ill patients requiring prolonged mechanical ventilation is expected to reach unprecedented levels over the next decade. Despite the prevalence, numerous distressing symptoms, and exceptionally poor outcomes associated with chronic critical illness, to date there is very limited scientific evidence available to guide the care and management of this exceptionally vulnerable population, particularly in LTACHs. Recent studies conducted in the traditional ICU setting suggest interprofessional, multicomponent strategies aimed at effectively assessing, preventing, and managing pain, agitation, delirium, and weakness, such as the ABCDEF bundle, may play an important role in the recovery of the chronically critically ill. This article reviews what is known about the chronically critically ill, provide readers with some important historical perspectives on the ABCDEF bundle, and address some controversies and practical implications of adopting the ABCDEF bundle into the everyday care of patients requiring prolonged mechanical ventilation in the LTACH setting. We believe developing

Keywords
► ABCDEF bundle
► chronic critical illness
► long-term acute care hospital
► pain
► sedation
► delirium

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new and better ways of addressing both the science and organizational aspects of managing the common and distressing symptoms associated with chronic critical illness and prolonged mechanical ventilation will ultimately improve the quality of life for the many patients and families admitted to LTACHs annually.

Advances in technology, ground-breaking research, and adoption of evidence-based practices have substantially improved intensive care unit (ICU) survival rates.[1,2] This improved survival, however, is often accompanied by a painful, protracted, and challenging course of recovery.[3–5] Chronic critical illness, now recognized as a distinct, complex syndrome of physiologic abnormalities and organ dysfunction,[6] is a devastating condition whose incidence is increasing to unprecedented levels.[3] Despite its incidence and human and financial costs, chronic critical illness has attracted surprisingly little interventional research and disturbingly few advances have been made to improve the care of this exceptionally vulnerable population. This is particularly true for the subgroup of chronically critically ill patients requiring prolonged mechanical ventilation (PMV) in the long-term acute care hospital (LTACH) setting.

As outlined in recent clinical practice guidelines from the *Society of Critical Care Medicine (SCCM)*,[7] pain, agitation, delirium, and weakness are major issues confronting critically ill patients, their families, clinicians, and payers. These common conditions, which generally remain poorly recognized and managed,[7–9] are now believed to play an important role in the multiple transitions and challenges critically ill patients encounter during the course of their recovery. Recent evidence generated in the traditional ICU setting suggests that the daily use of a multicomponent bundle that incorporates evidence-based interventions targeting pain, agitation, oversedation, delirium, weakness, and mechanical ventilation discontinuation, by an interprofessional ICU team, is feasible, safe, and improves patient-centered outcomes.[10] This evidenced-based strategy is referred to as the ABCDEF bundle (i.e., *A*ssess, prevent, and manage pain; *B*oth Spontaneous Awakening Trials (SATs) and Spontaneous Breathing Trials (SBTs); *C*hoice of analgesia and sedation; *D*elirium assess, prevent, and manage; *E*arly mobility and exercise; and *F*amily engagement and empowerment.)

While there is evidence suggesting that chronically critically ill patients frequently experience many of the same noxious symptoms as their acutely ill counterparts,[6] to date it remains unclear whether applying strategies such as the ABCDEF bundle *late* in the course of serious illness will reduce symptom burden and improve clinical outcomes. This article reviews what is known about chronic critical illness, provide readers with important historical perspectives on the ABCDEF bundle, and address controversies and practical implications of adopting the ABCDEF bundle into the routine care for patients requiring PMV in the LTACH setting.

Chronic Critical Illness, PMV, and LTACHs

The number of "chronically critically ill" (i.e., patients recovering from an extended ICU stay, PMV, and/or tracheostomy placement)[11] is expected to reach 600,000 within a decade with associated hospital costs nearing $60 billion annually.[12] Nearly all chronically critically ill patients report experiencing at least one distressing symptom (e.g., pain, fatigue, dyspnea, or thirst) during their course of their illness.[4,6,13–15] Severe functional and cognitive impairment is also common in this group,[3,14,16–20] with 90% of patients experiencing chronic partial muscle denervation[21] and as many as 74% having delirium and/or coma 6 months after hospital discharge.[14] Unfortunately, factors such as intubation, delirium, and oversedation frequently preclude chronically critically ill patients from being able to effectively communicate their needs and symptom experience.[13] Family and friends who function in a "caregiver" role are not immune to the toll of chronic critical illness, with many experiencing poor physical health, severe depressive symptoms, and severe financial stress.[18,22–24] The disturbances in family life are often substantial and permanent. For example, one study reported that after a prolonged ICU stay, some families needed to move to a less expensive home, declare bankruptcy, postpone educational plans, or delay medical care for another family member.[24]

Fewer than 10% of patients requiring PMV (i.e., a mechanical ventilation duration of at least 21 days)[25] are discharged directly home from the hospital.[11] While historically cared for in either traditional ICUs and/or step-down units, these patients are increasingly being managed in LTACHs.[3] Over a 5-year period from 2004 to 2009, the number of LTACH transfers more than doubled.[26] Either hospital based or free standing, LTACHs are centers that specialize in providing complex wound care, comprehensive rehabilitation, and mechanical ventilation discontinuation.[27] Originally created to facilitate discharge of medically complex patients from acute care hospitals,[27] it is estimated that the 412 U.S. LTACHs admit more than 130,000 patients and account for more than $5 billion in Medicare expenditures annually.[28,29]

Because of the debilitating nature of chronic critical illness, LTACH stays for patients requiring PMV are typically complicated and associated with several poor outcomes.[3,18–20,30] These outcomes include high 1-year mortality rates (44–77%),[18,19] severe functional impairment at LTACH discharge,[20] and diminished quality of life.[14,16–19,31] While returning home functionally independent is often an important goal for patients and their families,[30] this is a rather rare outcome in this population.[31]

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Rather, patients requiring PMV often experience multiple transitions in care in the year following their original hospital admission (median of four), which results in further costs and persistent, profound disability.[16] Caregivers of patients requiring PMV are also at risk for poor outcomes, as they were found to have higher depression scores than those reported for caregivers of patients with spinal cord injury, the aged, and patients with Alzheimer disease receiving respite care.[22]

Despite these disheartening findings, to date there is very limited scientific evidence available to help clinicians care for the chronically critically ill, particularly those requiring PMV in LTACHs.[28] It is also important to note that the relatively few studies that have been conducted in the LTACH setting are frequently limited by the use of administrative data alone and/or lack a comparable control group of chronically critically ill patients cared for in the traditional ICU setting. This begs the question of whether the poor outcomes associated with LTACHs are related to where care is delivered (i.e., traditional ICU vs. LTACH) versus the specific disease process (i.e., chronic critical illness). For example, researchers recently found that while older patients with chronic critical illness transferred to LTACHs invoked higher overall Medicare payments, they experienced similar survival compared with patients who remained in the traditional ICU setting.[17]

Chronically critically ill patients who require PMV share some common characteristics that may serve to influence both outcomes and health care delivery patterns. In general, they are older, sicker, and have more comorbidities than their acutely ill counterparts.[4,26] The most common medical conditions experienced by the chronically critically ill are acute respiratory failure requiring mechanical ventilation and sepsis.[26] Hospital-acquired infections are also pervasive, with over half of chronically critically ill patients admitted with sepsis experiencing this complication.[26] Single organ failure in this population is rare, with most chronically critically ill patients experiencing the effects of prolonged, severe, multisystem organ dysfunction/failure that commonly involves the neuroendocrine, respiratory, musculoskeletal, and immune systems.[5,32] Treatment of the multisystem organ failure seen in chronic critical illness is complex and often includes the use of complicated medication regimens, supportive therapies (e.g., hemodialysis, mechanical ventilation), numerous indwelling devices (e.g., urinary and central venous catheters), and several different consultative services.

Does Symptom Assessment and Management Influence Recovery from Critical Illness?

While many of the noxious symptoms experienced by the seriously ill were previously thought of as unfortunate and inevitable consequences of critical illness,[33] recent evidence suggests that the inappropriate management of these symptoms may not only contribute to the *development* of chronic critical illness but may also actually be *causal* to the poor outcomes experienced by this group.[7,26] Based on the results of a rigorous body of interventional clinical studies,[10,34–44] the *SCCM's Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium (PAD) in Adult Patients in the ICU*[7] currently advocate that pain, sedation, and delirium be routinely assessed; that strategies be employed to maintain patients in a wakeful or lightly sedated state; and that mobilization be employed early and often (see also ►**Table 1**).

Table 1 ABCDEF bundle–related pain, agitation, and delirium guideline recommendations

• Pain and delirium should be routinely monitored in all adult ICU patients
• Preemptive analgesia and/or nonpharmacologic interventions should be administered to alleviate pain in adult ICU patients prior to chest tube removal
• Intravenous (IV) opioids should be considered as the first-line drug class of choice to treat nonneuropathic pain in critically ill patients
• Either enterally administered gabapentin or carbamazepine, in addition to IV opioids, should be considered for treatment of neuropathic pain
• Thoracic epidural anesthesia/analgesia should be considered for postoperative analgesia in patients undergoing abdominal aortic aneurysm surgery
• Sedative medications should be titrated to maintain a light rather than a deep level of sedation in adult ICU patients, unless clinically contraindicated
• Early mobilization of adult ICU patients should be performed whenever feasible to reduce the incidence and duration of delirium
• Rivastigmine should not be administered to reduce the duration of delirium in ICU patients
• Either daily sedation interruption or a light target level of sedation should be routinely used in mechanically ventilated adult ICU patients
• Sleep should be promoted in adult ICU patients by optimizing patients' environments, using strategies to control light and noise, clustering patient care activities, and decreasing stimuli at night to protect patients' sleep cycles
• An interdisciplinary ICU team approach that includes provider education, preprinted and/or computerized protocols and order forms, and quality ICU rounds checklists should be used to facilitate the use of pain, agitation, and delirium management guidelines or protocols in adult ICUs

Source: Adapted from Barr et al.[7]

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One strategy for incorporating the PAD guideline recommendations into everyday care is use of the newly modified ABCDEF bundle.[33,44–46] While early versions of this bundle have proven safe, feasible, and effective when applied *early* in the course of critical illness in the traditional ICU setting,[10] to date it remains unclear whether applying the bundle *late* in the course of critical illness will reduce symptom burden and improve clinical outcomes in this extremely vulnerable group. It is possible that characteristics of both the chronically critically ill and LTACH setting would necessitate changes to the ABCDEF bundle. Moreover, the bundle itself has been recently revised to include more aggressive assessment, prevention, and management of pain and increased family engagement. Thus, it is important to consider both the level of evidence and history behind the ABCDEF bundle before deciding whether it can, or even should, be applied to patients who require PMV in the LTACH setting.

Evolution of the ABCDEF Bundle

Building the Evidence

Awakening-Protocolized Sedation and Spontaneous Awakening Trials

Over the past 15 years, several investigations focused on reducing sedative medication exposure among mechanically ventilated critically ill adults through two main strategies: protocolized sedation and/or daily SATs (aka daily sedation interruption [DSI]).[35,39,47] The use of either of these strategies has been shown to reduce the duration of mechanical ventilation, decrease ICU and hospital length of stay (LOS), and lead to a shorter time spent in coma, lower tracheostomy rates, and fewer complications.[35,39,48] Collectively, these early studies suggested that both protocolized sedation and SATs were safe and not associated with long-term harm.[36] We also know that maintaining patients in a lightly sedated, interactive state has important implications for their longer-term psychological health. For example, one study that compared the outcomes of patients managed throughout their ICU stay with a *light* versus *deep* sedation strategy found that light sedation was associated with a lower incidence of posttraumatic stress disorder (PTSD) symptoms, less trouble remembering ICU events, and fewer disturbing ICU memories.[49] This cumulative evidence led to the PAD guideline recommendation that either DSI/SATs or a light target level of sedation should be routinely used in mechanically ventilated adult ICU patients who require continuous intravenous (IV) sedative therapy.

Breathing

During the late 1990s, researchers demonstrated that interprofessional protocols facilitated mechanical ventilation discontinuation. Just as SATs have been used to promote wakefulness and reduce sedative medication exposure, SBTs were devised as a strategy to reduce the harmful effects of unnecessary mechanical ventilation exposure.[50] An interprofessional SBT protocol, when compared with physician-driven weaning in controlled studies, was shown to be safe and lead to a significantly shorter time to extubation.[51,52]

Awakening and Breathing Coordination

Given the demonstrated benefits of SATs and SBTs, Girard and colleagues rigorously evaluated a protocol that paired both interventions.[34] The intervention group in this randomized controlled trial (RCT) was managed with the "wake up and breathe" protocol, consisting of protocolized, *safety screen* and *success/failure criteria guided* SATs and SBTs, although the control group received SBTs and patient-targeted sedation according to "usual care." The daily SATs involved stopping continuously infused narcotics (as long as pain was controlled) and sedatives every day and, if needed, restarting either narcotics or sedatives at half the previous dose and titrating as needed. Patients treated with the combined protocol spent significantly more days breathing without ventilator assistance, were discharged from both the ICU and hospital earlier, had a shorter duration of coma, and were less likely to die compared with patients treated with a SBT strategy alone. For every seven people treated with the ABC approach, one life was saved at 1 year. Importantly, the proven benefits of the ABC protocol were not offset by adverse long-term cognitive and functional outcomes.[53]

Choice of Sedation and Analgesia

The past two decades have also marked important progress in our understanding of how the *choice* of sedative, particularly when protocolized or used in conjunction with a sedative reduction strategy such as SATs, affects patient outcomes.[38,54,55] Compared with the benzodiazepines, propofol with its short half-life and reduced volume of distribution is far less likely to accumulate and lead to persistent deep sedation or coma.[56] Compared with a continuous benzodiazepine sedation strategy, patients treated with dexmedetomidine experience more days alive without delirium or coma, more time at targeted sedation levels, fewer days on mechanical ventilation, and improved ability to communicate pain levels.[38,54,55] Current evidence also suggests that a nonbenzodiazepine sedation strategy (i.e., propofol or dexmedetomidine) when compared with a benzodiazepine strategy is associated with a reduced duration of mechanical ventilation, shorter LOS, and reduced health care costs.[57] This evolving evidence led the 2013 PAD guidelines to make a weak recommendation that a nonbenzodiazepine strategy is preferred over benzodiazepine strategy for mechanically ventilated adults.[7]

Delirium Monitoring/Management

At the same time that the hazards of deep sedation and delayed mechanical ventilation discontinuation were emerging, the importance of delirium, a form of acute brain injury characterized by an acute change/fluctuating course in baseline mental status and inattention, plus disorganized thinking or altered level of consciousness, was becoming apparent.[42,43,58,59] Occurring in up to 80% of mechanically ventilated patients[42,60] and nearly half of nonmechanically ventilated ICU patients,[61] delirium is sometimes preventable and associated with many serious adverse outcomes.[42,61–63] Both the occurrence and duration of delirium in the ICU are independently associated with increased short- and

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long-term mortality.[60,64,65] A recent meta-analysis[66] found delirious patients were 6 times more likely to experience complications, 2.5 times more likely to be discharged to skilled placement, had longer ICU and hospital LOS, and spent an average of 7 days longer on mechanical ventilation. Evidence now exists demonstrating that the impact of ICU delirium extends well beyond the period of acute hospitalization given that patients with delirium experience substantial functional decline,[67,68] a higher risk of rehospitalization,[69] and greater long-term neurocognitive impairment.[70–72]

The 2013 PAD guidelines advocate that all ICU patients should routinely be screened for delirium using a validated instrument such as the Confusion Assessment Method ICU[42] (CAM-ICU) or the Intensive Care Delirium Screening Checklist[73] (ICDSC). Without such assessments, clinicians miss up to 75% of cases of delirium, particularly if the patient is experiencing the predominately hypoactive form that is not accompanied by agitation.[7–9,74,75] Delirium screening should take place when patients are maximally awake (e.g., after an SAT) given emerging evidence that positive delirium assessments in the more sedated patient might not be as clinically important.[76]

Early Exercise/Mobility

A strategy for whole-body rehabilitation, achieved by the use of SATs, SBTs, and physical therapy–*driven early exercise and mobilization*, was found to be safe and well tolerated by mechanically ventilated patients over 5 years ago.[41] Patients treated with this strategy experienced significantly shorter duration of delirium and coma, had more ventilator-free days, and were more likely to return to independent functional status at hospital discharge than controls. Other more recent studies also found that active mobilization can be initiated safely in the ICU setting,[77] resulting in improved physical function,[77] reduced duration of mechanical ventilation,[78,79] shorter LOS,[79,80] and lower 1-year mortality.[78]

"Bundling" the Approach

Despite the rigorous evidence supporting the safety and efficacy of light sedation, SATs, SBTs, delirium monitoring/management, and early/exercise mobility, diffusion of these interventions into everyday clinical practice has been challenging.[33,81] Before the year 2010, one U.S. survey found that only 33% of intensivists used a valid delirium screening tool,[82] while others reported 30 to40% managed sedation without an arousal scale.[83,84] In the same time period, only 40% of ICU providers reported using SATs[84] and the rates of SBT use ranged from 31 to 42%.[84] Exercise and early mobility in the ICU were particularly underutilized, with one point prevalence study reporting that less than 2% of intubated patients were mobilized out of bed during their ICU stay.[85] While these findings may not be surprising to some clinicians, they highlight the gap that often exists between the publication of safe and effective clinical interventions and their adoption into daily ICU practice.

To address this adoption delay and provide a "tight, sticky message" to bedside clinicians regarding the hazards of ICU delirium and weakness, researchers at Vanderbilt University in 2010 suggested a novel "animation and liberation" program. "Liberation" aimed to reduce the harmful effects of sedative medication exposure through target-based sedation protocols, SATs, and SBTs. "Animation" referred to early mobilization, which was known to reduce delirium. This strategy was originally referred to as the *A*wakening and *B*reathing *C*oordination, *C*hoice of Medications, *D*elirium monitoring/management, and *E*arly mobility (ABCDE) bundle.[33,45,46,86,87]

Safety and Effectiveness of the ABCDE Bundle

While the safety and efficacy of the individual components of the ABCDE bundle are well established, until recently it remained unclear if the ABCDE bundle would also prove to be safe and effective if adopted into everyday ICU care. In a recent before–after study at one academic medical center, Balas and colleagues sought to address this important question and also identify the facilitators and barriers to ABCDE bundle adoption.[44] Among the 296 patients evaluated (146 pre- and 150 post-bundle implementation), postimplementation patients spent 3 more days alive breathing without mechanical ventilator assistance. After adjusting for age, sex, severity of illness, comorbidities, and mechanical ventilation status, patients managed with the ABCDE bundle were half as likely to experience delirium and were significantly more likely to be mobilized out of bed at least once during their ICU stay. The hospital mortality rate (pre-19.9 vs. post-11.3%, $p = 0.04$) was significantly lower in the group managed with the ABCDE bundle. Importantly, both self-extubation and reintubation rates were similar between the two groups. It is noteworthy that the positive effectiveness and safety outcomes reported occurred despite a lower-than-expected bundle compliance rate. While the proportion of patients where key ABCDE interventions were conducted significantly increased between the control group and the ABCDE group, the absolute increase in compliance was generally small. These results suggest that incremental improvements in ABCDE compliance are likely to continue to improve patient outcome across repeated quality improvement cycles.

Momentum for implementing an ABCDE bundle approach into everyday ICU care was also significantly aided by the recent support of several national quality and patient safety organizations. For example, in 2011 the *Institute for Healthcare Improvement's* Rethinking Critical Care (IHIRCC) program was established to reduce harm to critically ill patients by decreasing sedation, increasing monitoring and management of delirium, and increasing patient mobility.[88] A convenience sample of five "early adopters" of the ABCDE bundle was followed over the course of the program to document the process of improvement as well as outcomes. Each of these early adopters reported relative improvements in ICU average LOS (6–28%) and average LOS on the ventilator (3–25%). Other outcomes noted after ABCDE bundle implementation included improvements in sedation scores, percent of patients mobilized, and the number of delirium and sedation scores completed.

While not specifically focused on all aspects of the bundle, several other important studies have recently contributed to our increased understanding of the safety and effectiveness of an ABCDE approach to ICU management. For example, in a

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recent multicenter QI project conducted by the *Centers for Disease Control*, significant increases in SATs, SBTs, and percentage of SBTs performed without sedation were mirrored by significant decreases in duration of mechanical ventilation and hospital LOS.[89] Importantly, this group was also the first to report that increased SAT and SBT use was associated with both a significant decrease in ventilator-associated event risk per episode of mechanical ventilation and infection-related ventilator-associated complications. Another QI project focused on reducing the days of benzodiazepine exposure found this strategy led to an increase in the number of days patients spent alert and delirium free and an increased number of physical therapy/occupational therapy (PT/OT) treatments patients received while in the ICU.[90] Another before–after evaluation of a SAT/SBT protocol implementation effort in 702 patients significantly reduced the prevalence of delirium/coma and resulted in reduced sedation among critically ill patients.[91]

Implementing the ABCDE Bundle: Opportunities, Challenges, and Lessons Learned

Several important ABCDE bundle implementation barriers and facilitators have been identified in the literature (►**Table 2**). For example, the aforementioned IHI project highlighted the importance of utilizing pharmacists' expertise in developing protocols that emphasize an analgosedation approach to PAD management and removing lorazepam or continuous infusions from preprinted order forms. Other important implementation strategies included a focus on ensuring that sedation and delirium assessments are accurate, that targeted sedation scores are revised to reflect a more awake and engaged patient, and that a mobility team be established to facilitate early mobilization. In addition, key QI lessons learned from the IHI project included the importance of testing changes on a small scale (e.g., one patient, one time, starting with the easiest patients first), feeding back both process and outcome data regularly to ICU clinicians, providing education that is both sufficient and regular, and overcoming preconceived notions and traditions.

Table 2 Facilitators and barriers of successful ABCDEF bundle implementation[87,88,92]

Facilitators to adoption
Performance of daily interdisciplinary rounds
Engagement of key implementation leaders and garnering top-down leadership support
Sustained, diverse educational efforts
The bundle's quality and strength
Structural characteristics of the ICU
Organization-wide patient safety culture
ICU culture of quality improvement
Implementation planning/training/support and prompts
Early focus on "low-hanging fruit"
Realistic goal setting
Active reminders
Utilizing appropriate consultative services (e.g., psychiatry, occupational therapy)
Barriers to adoption
Intervention-related issues (e.g., timing of trials, fear of adverse events)
Communication challenges
Knowledge deficits
Workload concerns
Documentation burden
Excessive turnover
Staff morale issues
Excessive use of registry staff

Extending the Evidence: Importance of Assessing, Preventing, and Managing Pain and Family Engagement/Empowerment

Like most clinical improvement processes, the ABCDE bundle continues to evolve over time. One of the earliest criticisms of the bundle was the belief that it understated the importance of assessing, preventing, and managing pain. While the original ABC protocol did specifically allow for the administration\ of continuously infused opioids during the SAT process when active pain was present,[34] the misperception existed that pain medication should always be held during SATs and SBTs, regardless of whether pain is present. Given the prevalence and outcomes associated with unrecognized/undertreated pain,[7] this was accepted as a fair criticism and a misperception that should be addressed.

Another important fault of the original ABCDE bundle was that it tended to ignore the patient's family, a critical component of any ICU team. During critical illness, family members can help the patient make sense of the illness experience and support their loved one's psychological well-being by providing reassurance, hope, information, a sense of normality, and distraction from the ICU environment.[93–100] Families can also provide reorientation and are often the first to detect early signs of delirium.[101,102] For example, Black et al[101] tested the effect of a family psychological support intervention facilitated by nurses on delirium rates and psychological recovery. Intervention patients in this study showed less delirium than usual care (29–77%) and had significantly lower Sickness Impact Profile scores up to 12 weeks after the intervention. The use of diaries coauthored by health providers and family visitors with the intent of helping patients make sense of their memories and ICU experiences following discharge was also shown to decrease PTSD.[99]

While clinical trials have yet to characterize the precise benefit associated with active family involvement in ABCDEF bundle implementation, from a humanistic perspective the empowerment of family members to be equal participants in ICU patient care is clearly an appropriate goal of medical care (see discussion available for medical teams and families at www.icudelirium.org). Moreover, it is also possible that engaging family members in the care of ICU patients may lead to several other important outcomes including better

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recognition and treatment of PAD and weakness, delivery of important nonpharmacologic stress relieving and reorientation interventions (e.g., provision of human touch, music, sensory aids, family photos), enhancing ICU team performance by asking if certain interventions are being utilized, and more open and effective communication among patients and ICU clinicians.

In response to the aforementioned provider concerns, the terms associated with the letters A and B of the bundle have been changed and an additional letter (i.e., F) has been added (see ►**Fig. 1**). The *A* in the new ABCDEF bundle now refers to *A*ssess, prevent, and manage pain. While a patient's self-report of pain remains the gold standard, in the case where patients are unable to do so, the new bundle suggests clinicians utilize either the Behavioral Pain Scale (BPS)[103] or the Critical-Care Pain Observation Tool (CPOT).[104] The CPOT and BPS are both valid and reliable pain scales used to guide the assessment and treatment of pain in critically ill adults. The *B* in the bundle now stands for *B*oth SATs and SBTs. The term *both* was chosen purposively to reflect the importance of making sure these two interventions are used concomitantly given that the success of a SBT may be predicated by the completion of the SAT. Finally, the *F* in the bundle refers to *F*amily engagement and empowerment. This letter is used to emphasize the importance of family rounding, family visitation and the families' role in reducing delirium, provision of good end-of-life care, and effective transitional care.

Given the importance of the new PAD guidelines and the heightened interest in the ABCDEF bundle, the SCCM has devoted a substantial amount of time, talent, and resources to effectively disseminating and implementing this important bundle. A wealth of valuable information on this new initiative can be found at www.iculiberation.org. Here, those who are interested can find the most recent PAD guidelines, copies of the recommended PAD assessment tools, and links to upcoming events. Additionally, through the generous support of the *Gordon and Betty Moore Foundation*, the *SCCM* will soon select 60 hospitals (i.e., 20 in each of three regions around the country) for specific training in ABCDEF bundle implementation in an attempt to create lean, sustainable, and highly functioning interprofessional ICU teams that partner with patients and families to create a safe and comfortable ICU environment.

Controversies and Practical Implications of Adopting the ABCDEF Bundle into the Care of the Chronically Critically Ill in LTACHs

Overarching Issues

As Kahn and Carson describe, a lack of robust clinical trials conducted in the LTACH setting has forced LTACH administrators and clinicians to extrapolate the results of studies conducted in the traditional ICU setting and rely on their own clinical experience to define the standard that care should be delivered for patients requiring PMV in the LTACH setting.[28] Importantly, no studies have evaluated the safety and effectiveness of the new ABCDEF bundle in the LTACH setting. While intuitively it would seem that implementation of this bundle into the care of patients who require PMV in LTACHs might be safe and beneficial, there are several important factors that need to be considered before this assumption can be made.

Based on the lessons learned from the traditional ICU setting, it is clear that effective ABCDEF bundle adoption in the LTACH setting would be dependent on both individual (i.e., health care provider) and health system (i.e., LTACH) factors. Strong support and "buy-in" from LTACH administration would be needed to facilitate the necessary changes in the institutional culture that a multifaceted practice change requires. Preemptively addressing both the factors that will

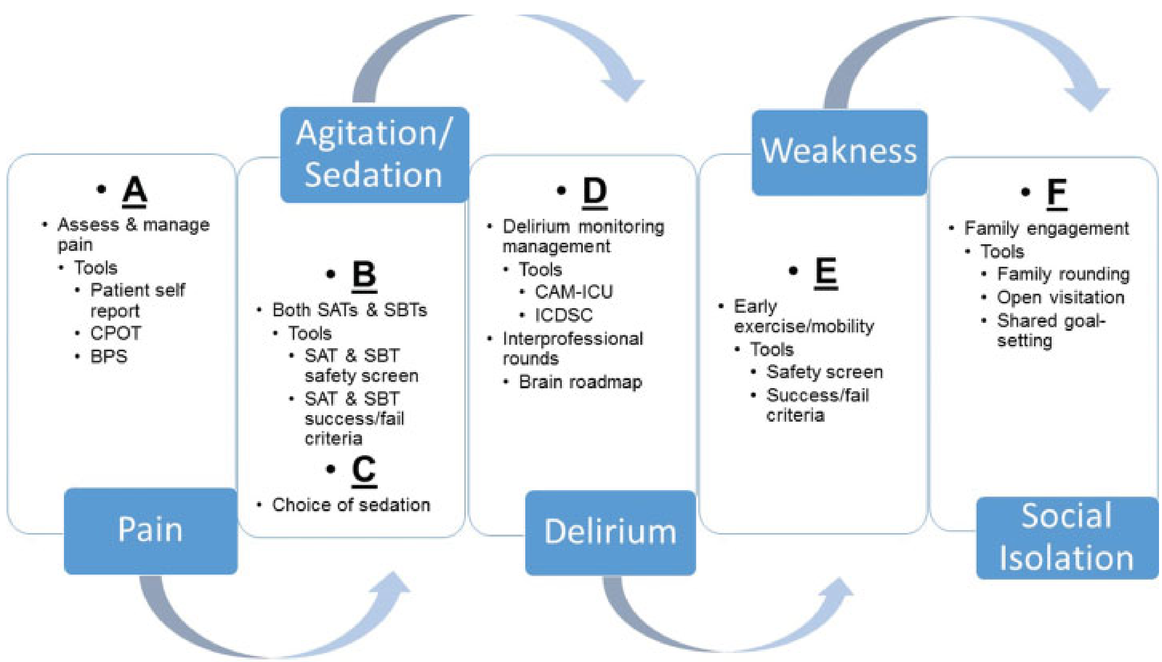

Fig. 1 ABCDEF bundle components and tools.

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facilitate bundle adoption as well as known barriers to its use (see ►**Table 2**) would be critical to the success of any LTACH ABCDEF bundle implementation effort.

Fortunately, there is reason to believe that many LTACHs do embrace the characteristics necessary for this type of system change. For example, one nation-wide system of LTACHs embarked on a QI initiative to establish a "*Ventilator Management and Weaning Best Practice*" effort.[102] Many of the best practice characteristics identified during the development of this QI project are nearly identical to those factors that are likely most important in the facilitation of ABCDEF bundle adoption in the LTACH setting. For example, the most successful weaning occurred in those LTACHs where a collaborative multidisciplinary plan of care was used in a consistent way on a 24/7 basis. Other important factors included constant team communication and collaboration, mutual respect for the contributions of all disciplines to the weaning process, and early intervention by rehabilitation services (see also ►**Table 3**).

The optimal level of staffing, resources, professional mix, and rounding patterns is an important issue to address before the ABCDEF bundle can be effectively implemented in the LTACH setting. Physical and occupational therapists, given their rehabilitation focus, will have an important role during implementation efforts, including the development of evidence-based mobilization protocols, identification of the optimal measurement tools to assess and monitor physical function, evaluation of the necessary equipment to support mobilization efforts, and identification of ways to best define and monitor safety-related outcomes. Speech/language therapists, currently more widely used in the LTACH than in the acute ICU setting, would be especially helpful in addressing the various communication and swallowing challenges experienced during PMV. They would also play an important role in further facilitating cognitive recovery, reducing aspiration risk, and expediting enteral nutrition. Most importantly, the use of a SLT may help facilitate the persons' participation in their own care and decision-making process by maximizing the opportunity to communicate and exert "free choice."[106]

While the role that pharmacists, nurses, and respiratory therapists play in ABCDEF bundle implementation in the traditional ICU setting has been described,[86,87] how these professions should function and interact in the LTACH setting remains unclear. There are known differences, for example, in nurse-to-patient staffing levels in the ICU versus LTACH setting (i.e., usually 1:2 vs. 1:4–6) that may prove challenging and necessitate changes in the ABCDEF bundle and the way it is implemented. The fact that the use of outsourced nurses is higher in the LTACH setting than in the ICU[107] may affect the type, intensity, and frequency of the ABCDEF-related training and education that is required. Finally, while care

Table 3 Similarities and differences in organizational elements needed for successful ABCDEF bundle implementation in ICU vs. LTACH settings

Facilitators of ABCDEF bundle implementation[44,105]	Facilitators of successful ventilator weaning in LTACH[102]
Strong administrative support	Leadership team had respect for one another's skills, knowledge, and abilities and possesses a single focus that supports the efforts and contributions of the various disciplines Administrative support, involvement, and clear expectations for productive, goal-driven patient care conferences Provided sufficient time for physicians and staff to participate in care conferences
Performance of interdisciplinary rounds	All clinicians had a clear understanding and acceptance of every discipline's role, contribution, and value in the process
Engagement of key implementation leaders	Care conference leader who can focus the team, assure documentation of a multidisciplinary plan for all patients that is followed and monitored by all team members
Sustained, diverse educational and implementation efforts	Provision of multidisciplinary education programs related to ventilators and ventilator management that recognize and use the expertise of respiratory therapy staff
Organizational wide quality and patient safety culture	Use of advanced practice nurse, case manager, or utilization review coordinator to monitor and facilitate patient progress toward a timely discharge
Reduced workload and efficient documentation	Appropriate staffing patterns to support "24/7" weaning, allowing continual monitoring of patients for tolerance, anxiety, and fatigue are supported philosophically as well as financially Consistent numbers of respiratory therapy staff 24 h/d, flex staffing to support changes in numbers of mechanically ventilated patients Licensed nurse (RNs and LPNs) patient ratios of 1:4 to 1:6
Low turnover, high staff morale, and less use of registry staff	Retention programs and strategies to retain experienced staff, assure staff are satisfied, motivated, and feel valued by the organization

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coordinating conferences are common in most LTACHs, these conferences are more likely to occur weekly rather than the daily rounding and quality checklist generation that occurs in most traditional ICUs.[108] Ideally, for effective bundle implementation in the LTACH setting, rounding would occur at least once a day and include those professions responsible for intervention delivery and assessment. At a minimum, this would include the patients' nurse, respiratory therapist, pharmacist, physical therapist, and physician/advanced practice provider. A template of an ABCDEF bundle–related rounding tool is provided in ►**Table 4**.

The success of any QI effort, such as the ABCDEF bundle implementation, requires standardization. The pain, sedation, and delirium assessment tools that are most valid, reliable, and appropriate for specific populations (e.g., patients requiring PMV) will need to be identified. Moreover, the frequency of each assessment and the personnel best suited for their administration and documentation will need to be defined. How and where the results of the SAT, SBT, and early mobilization safety screen and success/failure criteria will be documented will also need to be determined.

Intervention-Related Knowledge Deficits and Practical Implications

Assess, Prevent, and Manage Pain

Until the epidemiology of pain in the LTACH setting is better understood, it must be assumed that pain is as ubiquitous and poorly controlled as it is in most acute care ICUs.[7] Among LTACH patents requiring PMV, while levels of wakefulness and thus the ability of patients to self-report pain is likely to be greater than that of the ICU, some LTACH patients will still be unable to effectively communicate pain due to a delay in tracheostomy decannulation or cognitive impairment (i.e., delirium). Although findings from several studies suggest that verbal complaints of pain among cognitively impaired individuals are reliable and valid, verbal reports of pain generally decrease as the degree of cognitive impairment increases.[109] We also know that clinical staff often discount complaints of pain in persons with cognitive impairment because of inconsistent pain reports, thus elevating the risk for the under-recognition and undertreatment of pain.[109] Although non-verbal ICU pain scales such as the CPOT or the BPS have yet to be validated in the LTACH setting, their utility in the context of critical illness has been demonstrated. Finally, we would suggest that LTACH clinicians should not rely solely on nonspecific symptoms of pain (e.g., tachycardia, hypertension, or generalized agitation) when characterizing the level of pain in this subpopulation given the multitude of factors that may affect these conditions.

In the ICU setting, parenteral opioids such as fentanyl, morphine, and hydromorphone are often administered as continuous infusions. These medications are the mainstay of pain (and sometimes sedation) management, given the ease by which these agents can be titrated and the frequent lack of reliable oral or enteral access in this population. In the LTACH setting, the decreased availability of continuous bedside monitor usually precludes the used of continuous IV opioid infusions. Moreover, given that most patients requiring PMV have a reliable enteral method of medication administration and the fact that levels of pain in this setting may be more chronic and consistent, oral (enteral) morphine, oxycodone, and hydromorphone are the mainstays of opioid therapy in the LTACH setting. Sustained release opioid formulations should never be crushed and administered via a gastric or enteral tube. When administered orally (enterally), opioids undergo first-pass metabolism and thus have a duration of action that far exceeds that of IV formulations thus facilitating administration 4 to 6 hour/day. With the onset of action of oral opioids rarely exceeding 15 minutes, they can often replace IV opioids for the treatment of breakthrough pain. The QTc interval should be measured at least weekly with a 12-lead ECG for any patient receiving chronic methadone therapy. A fentanyl patch can alternatively be applied to a patient with chronic pain who does not have functioning gut access, although it is important to note that fentanyl patch takes 12 hours to start working and continues to deliver fentanyl for 12 hours after patch removal given the depot effect that is created.

A prior use of high-dose opioid therapy in the ICU for periods longer than 1 week should inform all LTACH opioid prescribing decisions regardless of the level of pain documented. Opioid withdrawal reactions may mimic the symptoms of other syndromes such as delirium and should be managed with a tapering dose of scheduled opioid therapy over at least a week. LTACH clinicians should define opioid dosing requirements using both clinical assessment and the recommendations from equianalgesic opioid conversion

Table 4 ABCDEF bundle daily rounding tool

A—Results of previous 24-h pain assessments. Incorporation and reporting of nonpharmacologic and pharmacologic pain management strategies
B—Results of SAT and SBT safety screens and trials including target and actual RASS/SAS ratings
C—Review of current medication list and identification of any potentially deliriogenic medications (e.g., anticholinergics, benzodiazepines)
D—Results of previous 24-h delirium assessments
E—Results of early mobility safety screen and trial. Current activity level
F—Did family visit with patient in past 24 h? When were they last updated on plan of care? Do they have any concerns? Include in rounds as able and they can be empowered to help keep the team aware of components of the ABCDEFs that were not performed

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guidelines for all new LTACH admissions (or patients who were temporarily readmitted back to the acute care ICU). Although non-opioid analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticonvulsants are frequently used in the LTACH setting to avoid the safety concerns associated with opioids (e.g., constipation, respiratory depression) data supporting the use of these agents in the LTACH setting are sparse and the NSAIDs must be used with caution in this site given the increased risks for bleeding and renal insufficiency that may occur in frail populations such as the chronically critically ill.

Both SATs and SBTs

While patients receiving PMV do consume high cumulative amounts of sedatives, opioids, and antipsychotics over the course of their LTACH stay,[110] it is rare for either sedatives or opioids to be administered as a continuous IV infusion in this setting. It should be noted that oral (enteral) or single-dose IV administration of opioids and/or benzodiazepines can still reduce wakefulness, the ability to follow simple commands and respiratory drive will affect the ability to conduct a successful SBT. Clinicians should therefore consider a patient's current status and the requirements of the SBT screen before administering opioid or benzodiazepine therapy before all planned SBTs. Research is required on how SAT and SBT screening and success criteria should be adjusted from what is currently in the ICU for patients with PMV being managed in the LTACH.

Given the lack of empiric evidence for the benefits of SATs in the setting of PMV, several important factors would need to be considered before their adoption into routine care. First, it would be necessary for health care providers to have the training and education necessary to use valid, reliable, and objective measures of a patient's sedation level to guide the awakening process. As suggested in the new SCCM guidelines, both the Richmond Agitation-Sedation Scale[111] (RASS) and Sedation Agitation Scale[112] (SAS) are the most valid and reliable sedation assessment tools for measuring both the quality and depth of sedation in various clinical situations involving adult ICU patients. While it is unclear exactly how many LTACHs currently use either of these tools, given the experience in traditional ICUs their adoption into care can be accomplished with minimal time and training. Next, considering how long chronically critically ill patients may have been exposed to sedatives (in particular the benzodiazepines) in the acute care setting, it will be very important for staff in the LTACH setting to closely monitor their patients for signs of acute withdrawal syndrome should SATs be utilized. In fact, this may be an important question to ask to the transferring facility prior to LTACH admission. Finally, when developing a SAT protocol, it will be important for the LTACH to consider what should be incorporated in the SAT safety screen and success/failure criteria. Some example criteria, which have been used in prior studies in the acute care setting, are provided in ►**Table 5**.

Until very recently, there was little information regarding the role of SBTs in the context of PMV. Traditionally, the process of liberating patients from PMV was divided into two phases: (1) identifying and correcting, if possible, the physiological barriers to weaning and (2) applying a systematic approach to ventilator discontinuation.[114]

One recent, single-center RCT conducted in patients requiring PMV in the LTACH setting compared weaning duration between patients managed with pressure support with those managed with unassisted breathing through a tracheostomy collar.[113] Patients were included in the study if they received mechanical ventilation for at least 21 days and excluded for the following reasons: cardiopulmonary instability, profound neurological deficits, bilateral phrenic-nerve injury, previous admission to the LTACH, and a life expectancy of less than 3 months. Patients randomized to the pressure support arm received gradual systematic reductions in pressure support as tolerated. Patients randomized to tracheostomy collar were disconnected from the ventilator each morning and allowed to breathe on their own through their tracheostomy (i.e., similar to a SBT). During the first 2 days of the protocol, the SBT group was reconnected to the ventilator at night and assist-control ventilation was instituted for the next 12 hours.

Patients managed with the tracheostomy approach had a shorter weaning time and, after adjustment for baseline covariates, were more likely to be successfully weaned (hazard ratio [HR] = 1.43; 95% confidence interval [CI]: 1.03–1.98; $p = 0.03$). Although survival rates at 6 and 12 months were similar between the two groups, this study is important for LTACH clinicians given that it is the first to provide empirical support for the use of SBTs (albeit different from SBT protocols seen in the acute care setting) in the context of PMV.[28]

One of the most interesting findings of this study, however, was what occurred immediately before the randomization process. In this time period, 500 patients underwent a screening procedure that consisted of unassisted breathing via a tracheostomy collar for up to 5 days. A total of 160 (32%) patients passed this initial tracheostomy challenge and thus were unable to be randomized into the study. This finding strongly suggests that many LTACH patients may be ready to be liberated from the ventilator much earlier than expected.

Choice of Sedation

Agitation is frequent among LTACH patients requiring PMV and has been shown to be greater among patients at the time of LTACH admission who are less severely ill, are transferred from an academic medical center (vs. a community hospital), had delirium, and who had benzodiazepine therapy discontinued at the acute care hospital.[115] Every effort should be made to identify the source of agitation in any LTACH patient requiring PMV before a sedating medication is administered given that common sources of agitation such as pain, delirium, hypoxemia, sleep disturbances, and acute infection are not likely to respond to the administration of a sedative medication such as a benzodiazepine. Patients who are anxious should receive constant reassurance from clinicians and family. Agitation from a withdrawal reaction from the chronic use of an opioid or benzodiazepine at the acute care hospital should always be investigated. Low-dose oral (enteral) therapy with diazepam that is slowly down-titrated

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Table 5 Potential SAT, SBT, and exercise/mobilization safety screen and success failure criteria for patients requiring prolonged mechanical ventilation in the LTACH setting[44,113]

SAT safety screen criteria
A patient will be ineligible for a SAT if any of the following criteria are met:
1. Active seizures
2. Acute alcohol/benzodiazepine withdrawal
3. Use of neuromuscular blockade
4. Suspected elevated intracranial pressure
5. Documentation of myocardial infarction in past 24 h
6. Current RASS score >2
SAT success/failure criteria
A SAT will be considered a failure should the patient display any of the following criteria:
1. RASS score >2 for >5 min
2. Pulse ox $<88\%$ for >5 min
3. Respirations >35 BPM for ≥ 5 min
4. Acute cardiac arrhythmia
5. Two or more of the following: heart rate increase ≥ 20 per minute BPM, heart rate <55 BPM, use of accessory muscles, abdominal paradox, diaphoresis or dyspnea
SBT safety screen criteria
A patient will be ineligible for a SBT if any of the following criteria are met:
1. Cardiopulmonary instability as reflected by:
a. Requiring vasopressor support (e.g., dopamine >5 μg/kg/min)
b. Oxygen saturation as measured by pulse oximetry (SpO_2) $<90\%$ with fractional inspired O_2 concentration (FIO_2) >0.40 and PEEP >5 cm H_2O
2. Profound neurological deficits (defined as Glasgow coma scale < 7)
3. Bilateral phrenic-nerve injury
4. Life expectancy less than 3 mo (e.g., metastatic cancer that has not responded to medical or surgical therapy)
SBT success/failure criteria
A SBT will be considered a failure should the patient display any of the following criteria:
1. Heart rate $>$ [(220-age) $\times$ 0.8] beats/min
2. Systolic pressure $<$ 80 mm Hg
3. $SpO_2 < 90\%$
4. Patient request
5. Two of the following criteria simultaneously: respiratory rate $>$ 35 breaths/min, systolic pressure $>$ 180 mm Hg, agitation as reflected by the inability to remain motionless for 1 min, diaphoresis
Exercise safety screen criteria
A patient will be ineligible for exercise/mobilization if any of the following criteria are met:
1. RASS score < -3
2. $FIO_2 > 0.6$
3. Set PEEP >10 cm H_2O
4. Increasing doses of vasopressor infusions in the past 2 h
5. Evidence of active MI
6. Administration of a new antiarrhythmic agent
7. Receiving therapies that restrict mobility (e.g., wound vacuum, open-abdomen)
Injuries in which mobility is contraindicated (e.g., unstable fractures)
Exercise success/failure criteria

(*Continued*)

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Table 5 (*Continued*)

An exercise session will be considered a failure should the patient display any of the following criteria:
1. Symptomatic drop in mean arterial pressure
2. Heart rate <50 or >130 BPM ≥ 5 min
3. Respiratory rate <5 or >40 BPM ≥ 5 min
4. Systolic blood pressure >180 mm Hg ≥ 5 min
5. Pulse oximetry reading $<88\%$ ≥ 5 min
6. Marked ventilator dyssynchrony
7. Patient distress
8. New arrhythmia or evidence of active MI
9. Concern for airway device integrity or endotracheal removal
10. Fall to knees

Abbreviations: BPM, breaths per minute; LTACH, long-term acute care hospital; PEEP, positive end-expiratory pressure.

over a 10- to 14-day period should be employed in all situations where persistent agitation related to benzodiazepine withdrawal is likely.[116] In all other instances, the use of benzodiazepine therapy in this population should be very limited, given that will increase the risk for delirium and falls. Antipsychotics should not be administered for the treatment of agitation in patient without delirium, given the many safety concerns with the chronic use of these agents. In patients in whom a clear source for their agitation is not identified, nonpharmacologic interventions like a sitter or restraints may sometimes need to be temporarily instituted.

Delirium Assessment, Prevention, and Management

The fact that coma, delirium, and depression are prevalent among LTACH patients requiring PMV may not be surprising given the acuity, age, and high psychoactive medication use in this population.[117,118] Among one cohort of 478 patients admitted to a LTACH for PMV, 142 (30%) had persistent coma and/or delirium and were unable to ever be evaluated for depressive disorders. Of the remaining 336 patients, 142 (42%) were diagnosed with depressive disorders. The presence of a depressive disorder was associated with a significantly higher rate of weaning failure and was independently associated with higher mortality. The fact that the LTACH LOS was significantly higher among patients with delirium suggests that these symptoms should be regularly evaluated in the LTACH setting. As noted previously, both the CAM-ICU and ICDSC are valid and reliable delirium assessment tools for use with mechanically ventilated patients.

Reversible, preventable causes for delirium should always be identified in the LTACH setting. Nonpharmacologic strategies, including reorientation, use of hearing aids, environmental modifications, and early mobilization, may help reduce the burden of delirium in this setting. Sleep promoting strategies that include the ear plugs and the occasional use of non-benzodiazepine sleep aids may also reduce the incidence of delirium. Administration of scheduled antipsychotic therapy to prevent or treat delirium in LTACH patients requiring PMV is common despite the lack of any evidence that antipsychotic therapy prevents delirium or improves the outcome of delirium in either ICU or LTACH populations.[117,119] One recent evaluation of LTACH patients requiring PMV found that among the 39% of patients, scheduled antipsychotic therapy was administered on 52% of the LTACH admission days and was independently associated with a significantly greater incidence of delirium, psychiatric evaluation, and sitter use. While antipsychotic therapy may have a role for those LTACH patients with more severe delirium-associated symptoms (e.g., hallucinations, agitation), their current risk:benefit ratio does not support routine use and thus the continued use of antipsychotic therapy for any patient requiring PMV who is transferred to the LTACH should always be questioned.

Early Mobility/Exercise

Most patients admitted to medical center-based ICUs who require PMV and survive the initial catastrophic episode of shock, respiratory failure, or overwhelming infection are often lost to follow-up upon transfer from the medical center to the community LTACH. Often, physical rehabilitation is deescalated in the LTACH rather than advanced due to the frailty, multiple comorbidities, chronic disability of older patients, and limited LTACH resources. This situation results in regression of any functional or physical gains achieved in the medical center, and accelerates a downward spiral toward nursing home care. There are a few small studies that compare progressive, intense physical rehabilitation to usual care,[120] in chronically critically ill, ICU survivors in the LTACH setting; and none of these have modified current standards of care. Thus, these patients have extended LTACH stays that frequently lack goal-directed physical therapy to meet the rehabilitation needs of many ICU survivors. Recently, several epidemiologic studies revealed the magnitude of economic strain and resource allocation required in caring for this growing population.[3,16,17] Although some LTACH patients may not meet rehabilitation criteria, the lack of evidence-based studies and resources have limited a more aggressive approach toward the rehabilitation of these patients.

One of the major barriers to conducting effective mobility-based rehabilitation in the LTACH population is the profound

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degree of weakness and disability of this population, which precludes their ability to participate in the majority of physical therapy maneuvers, let alone walk. One small pilot study functionally assessed 14 older survivors of critical illness requiring PMV in a university-based LTACH, using a battery of validated measures of strength (handgrip), physical performance battery (SPPB), mobility (gait speed), balance, and coordination (short and endurance [6-minute walk], estimated VO_2 by upper extremity bicycle ergometry).[121] This functional testing demonstrated weakness (handgrip $= 20 \pm 8$ kg, $n = 9$; reference $= 45 \pm 8$ kg men, 28 ± 6 women[122]), impaired balance and coordination[123] (SPPB score $= 4$, $n = 9$, severe disability <8), poor mobility (gait speed $= 0.26 \pm 0.30$ m/s, reference >1 m/s[124]), and low endurance (6-minute walk distance $= 57 \pm 126$ ft, $n = 5$, reference $= 2{,}070 \pm 305$ ft[125]; and estimated $VO_2 = 6.1 \pm 1.2$ mL/kg/min, $n = 4$, reference 27–31 mL/kg/min; METS 1.8 ± 0.3). These results contextualized these patients' severe weakness, functional impairment, and disability but more importantly demonstrated feasibility in rehabilitating these patients.

A rehabilitation protocol which addresses these patients' severe disability and immobility best allows for LTACH patients of varying functional ability to perform exercise maneuvers (►**Table 6**). When combined with achieving strenuous targeted effort goals, the incorporation of exercise protocols similar to this have demonstrated improvements not only in functional outcomes (activities of daily living, basic mobility, i.e., rolling and sit to stand) but also in clinical outcomes such as decreasing ventilator days, increasing weaning success, and discharge home.[126] Thus, the incorporation of patient-oriented rehabilitation protocols may be key to effectively introducing the "early mobility" principles of the ABCDEF bundle into the LTACH setting.

Family Engagement/Empowerment

Given the known physical, psychological, and financial stress that caregivers experience, it is important to consider how best to engage patients' family members effectively in the care of their loved ones while they are in the LTACH setting. While this is in evolution and certainly a focus of the SCCM's ICU Liberation collaborative program (www.ICUliberation.org), there are certain concepts that have already been emphasized and embraced by patients and families during and following the ICU experience. Rather than repeat them here, we refer the reader to the following: http://www.icudelirium.org/family.html.

Conclusion

Developing new and better ways of managing the common and distressing symptoms associated with chronic critical illness had great potential to improve the quality of life for the large number of patients admitted annually to LTACHs. While yet to be tested in the LTACH setting, there is evidence from the traditional ICU setting that the ABCDEF bundle may possibly improve the care and outcomes of the chronically critically ill. We have discussed elements of this care bundle that would be logically adapted for use in the LTACH setting

Table 6 Simplified exercise protocol for LTACH patients requiring PMV

	Bed dependent	Chair dependent	Ambulatory
Muscle strengthening (functional)	Leg pressure Hip extension/abduction (supine) Closed kinetic terminal knee extension Ankle dorsiflexion Proprioceptive Neuromuscular facilitation Scapular depression Lat pulls Triceps Hand putty	Modified sit to stand Modified step ups Hip extension/abduction (standing) Closed kinetic terminal knee extension Ankle dorsiflexion Proprioceptive Neuromuscular facilitation Shoulder flexion/abduction Lat pulls Triceps Hand putty	Squats Step ups Hip extension/abduction (standing) Lat pulls Deltoid flies Triceps Biceps Hand putty
Muscle endurance	Sitting edge of bed (30–60 s rhythmic stabilization) Leg press (30 s) Supine leg raise (reverse) (30 s)	Restorator (30–60 s) Upper and lower extremity Standing balance: Unilateral stance Rhomberg Modified sit to stand Modified step up	Stationary bicycle (60–90 s) Upper body ergometry (60–90 s) Squats Step ups Modified military press Triceps
Aerobic	Wheelchair mobility	Stationary bicycle Upper body ergometry Ambulation	Treadmill Stationary bicycle Upper body ergometry Ambulation

Abbreviations: LTACH, long-term acute care hospital; PMV, prolonged mechanical ventilation.
Note: A protocol developed for all mobility levels to allow all patients to benefit from rehabilitation that addresses all aspects of fitness (muscle strengthening, muscle endurance, and aerobic capacity).

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within the context of appropriately designed research and quality improvement studies monitoring for safety and effectiveness. This article was written to propose a role for such an interprofessional interventional approach to the care of the thousands of patients suffering from chronic critical illness.

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CRITICAL CARE

REVIEW Open Access

A conceptual framework: the early and late phases of skeletal muscle dysfunction in the acute respiratory distress syndrome

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Abstract

Patients with acute respiratory distress syndrome (ARDS) often develop severe diaphragmatic and limb skeletal muscle dysfunction. Impaired muscle function in ARDS is associated with increased mortality, increased duration of mechanical ventilation, and functional disability in survivors. In this review, we propose that muscle dysfunction in ARDS can be categorized into an early and a late phase. These early and late phases are based on the timing in relationship to lung injury and the underlying mechanisms. The early phase occurs temporally with the onset of lung injury, is driven by inflammation and disuse, and is marked predominantly by muscle atrophy from increased protein degradation. The ubiquitin-proteasome, autophagy, and calpain-caspase pathways have all been implicated in early-phase muscle dysfunction. Late-phase muscle weakness persists in many patients despite resolution of lung injury and cessation of ongoing acute inflammation-driven muscle atrophy. The clinical characteristics and mechanisms underlying late-phase muscle dysfunction do not involve the massive protein degradation and atrophy of the early phase and may reflect a failure of the musculoskeletal system to regain homeostatic balance. Owing to these underlying mechanistic differences, therapeutic interventions for treating muscle dysfunction in ARDS may differ during the early and late phases. Here, we review clinical and translational investigations of muscle dysfunction in ARDS, placing them in the conceptual framework of the early and late phases. We hypothesize that this conceptual model will aid in the design of future mechanistic and clinical investigations of the skeletal muscle system in ARDS and other critical illnesses.

Introduction

Improvements in general critical care and ventilator management of acute respiratory distress syndrome (ARDS) over the past four decades have led to a significant reduction in mortality, from 80 % in the initial reports to the current rate of 20 % to 30 % reported in clinical trials [1]. These trends have resulted in a growing number of ARDS patients who are ICU survivors: approximately 200,000 people per year in the United States alone [2]. Unfortunately, these patients commonly have lasting sequelae, including increased mortality [3–5], physical and cognitive impairment [6–8], and reduced quality of life [9]. With the introduction of such outcomes in clinical trials, the skeletal muscle system has been increasingly recognized as a major target organ in ARDS. Clinically apparent skeletal muscle weakness in the critically ill, termed ICU-acquired weakness (ICUAW) [10, 11], occurs in up to 60 % of patients and is independently associated with mortality [12, 13].

We propose, on the basis of observations of animal models and clinical studies, that muscle wasting in patients with ARDS can be divided into early and late phases. These phases differ in pathophysiology and potential underlying mechanisms and can be identified by their relationship to the time course of lung injury, recovery, and resolution. In this review, we will summarize major recent findings regarding clinical and mechanistic investigations into muscle wasting in ARDS and frame them in the context of the early and late phases. We propose that this conceptual framework will enhance the

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design of future clinical and mechanistic investigations and aid in tailoring therapies designed to treat muscle wasting in ARDS.

ARDS is the more severe end of the spectrum of diseases requiring admission to an ICU. Although the muscle-wasting response of patients with ARDS has not been explicitly compared with that of critically ill patients without ARDS (that is, sepsis), patients with ARDS appear to have a very high incidence of ICUAW (up to 60 %) [12–15]. While the animal studies offer some clues to mechanistic differences between muscle wasting in ARDS and sepsis [16], further carefully controlled human studies are needed to determine whether clinical differences exist in the muscle injury and recovery trajectories of sepsis patients with and without concomitant ARDS. For these reasons, in this review, we will focus primarily on muscle wasting in ARDS, although we feel that this paradigm may prove useful in other critical illnesses, such as sepsis.

The diagnosis of intensive care unit-acquired weakness

Since the original report by MacFarlane and Rosenthal [17], muscle wasting associated with critical illness has been called acute quadriparetic myopathy, thick filament myopathy, critical illness myopathy, critical illness polyneuropathy, and ICU-acquired paresis, among other terms. These names reflect the varying associated pathologic and electrophysiologic characteristics. The nomenclature has recently been simplified, and the term ICUAW signifies clinically measureable weakness in a critically ill patient without other known precipitating factors causing nerve or muscle injury [10, 11].

The diagnosis of ICUAW is made by using either manual muscle testing (MMT) or grip strength meters and by using specified cutoff values to denote weakness. Unfortunately, MMT is effort-dependent and insensitive and likely under-represents the degree of muscle dysfunction present in these patients [18–20]. MMT, grip strength meters, and hand-held dynamometers also all lack the ability to clearly discern muscle fatigability, which may contribute to the long-term functional impairments in ICU survivors. Other functional tests - such as the short physical performance battery [21], six-minute walk distance [8], or walk speeds [22] - may provide more information about global function, although these composite functional tests can be affected by factors other than muscle dysfunction and require a cooperative, engaged patient.

Given the limitations of these volitional measurements of muscle function in critically ill patients and survivors, other methods for identifying ICUAW are needed. Nerve conduction and direct muscle stimulation may improve the sensitivity of diagnosing ICUAW in the non-cooperative patient [23] but are infrequently used at present. Skeletal muscle ultrasound is a promising modality that can non-invasively identify the loss of muscle mass in critically ill patients; muscle echointensity values may yield additional functional information [24, 25]. These modalities remain promising, although further research is needed in this area.

Systemic ‘biomarkers’ of ICUAW would also be helpful in identifying ICUAW. Creatine phosphokinase, the most common laboratory test used for identification of myositis in other contexts, is not helpful in identifying patients with ICUAW [11, 15]. In a pilot study, peak plasma neurofilament levels were higher in patients with ICUAW, but peak levels were not reached before patients could engage in MMT, limiting the utility of this as a biomarker [26]. Another study of post-cardiac surgery patients found that insulin-like growth factor 1 (IGF-1) levels were suppressed in patients who developed ICUAW but that growth and differentiation factor 15 levels were elevated [27]. Additional studies are needed to identify systemic biomarkers that can reliably identify patients at high risk for developing ICUAW. Identifying such patients may assist in targeted allocation of physical therapy or future pharmacologic interventions.

Phases of muscle dysfunction in acute respiratory distress syndrome

Definition of the early phase

The early phase of muscle dysfunction, which occurs hours to days after the onset of illness, begins with the activation of acute lung and systemic inflammation characteristic of early lung injury. We define the early phase to begin with the onset of the acute illness and terminate when the acute inflammation-driven muscle atrophy program resolves (Fig. 1), usually within days.

Muscle atrophy is the predominant and characteristic feature of early-phase muscle dysfunction and is driven primarily by (a) acute systemic inflammation and (b) limb and diaphragmatic muscle disuse from enforced bed rest and mechanical ventilation, respectively. Nerve, neuromuscular junction (NMJ), or direct myofiber injury or a combination of these may variably initiate atrophy or contribute to muscle weakness during the early phase. Considering the ubiquity of inflammation- and immobility-induced atrophy in these patients, we hypothesize that all patients with ARDS experience early-phase muscle wasting. We propose that atrophy is the most universal feature of ICUAW, although other pathologies such as inflammatory myopathies, polyneuropathies, or combinations also occur. Factors such as age, illness severity, organ failures, medications, malnutrition, and hypoxia may drive the severity or type of muscle dysfunction in an ancillary fashion. The drivers and clinical significance of these differing phenotypes are poorly understood. However, it is clear that

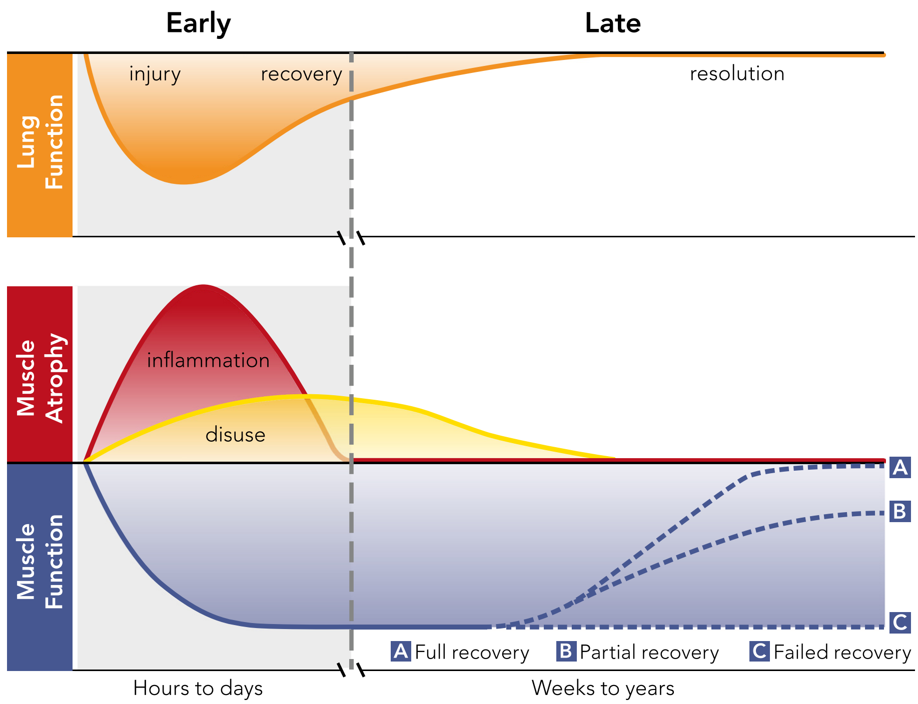

Fig. 1 The early and late phases of muscle wasting in acute respiratory distress syndrome. The early phase of muscle wasting begins with the onset of lung injury and is caused by lung and systemic inflammation and to a lesser degree disuse, both leading to muscle atrophy. The late phase of muscle wasting begins as lung function recovers and acute systemic inflammation resolves. Disuse continues in many patients during the late phase. Muscle function deteriorates in the early phase, and dysfunction persists in many patients during the late phase, which may last for years despite resolution of lung injury and cessation of ongoing muscle atrophy. Factors mediating recovery trajectories in the late phase are poorly understood

both limb [12] and diaphragmatic [28, 29] muscle weakness, regardless of the pathophysiology, independently contribute to early-phase mortality.

Definition of the late phase

The late phase of muscle dysfunction begins following resolution of the early acute lung and systemic inflammation characteristic of the early phase, usually following the first few days of illness and during the recovery phase of lung injury. Muscle atrophy may continue into the late phase, driven by disuse, but this factor usually resolves once patients are no longer bedridden. Similar to early-phase wasting, late-phase muscle weakness may occur from persistent or unresolved nerve or NMJ injury [30, 31].

The characteristic feature of late-phase muscle wasting is that muscle dysfunction persists despite recovery and resolution of lung injury in many patients [8, 20]. Factors such as age, baseline (pre-ARDS) muscle function, medications administered during or after the ICU stay, comorbidities, route of muscle injury (nerve versus NMJ versus myofiber), and nutrition may contribute to both the degree of injury and the rate of muscle functional recovery. However, the clinical characteristics associated with complete, partial, or failed recovery of muscle function in ARDS survivors (Fig. 1) are generally poorly understood.

One fundamental question is whether the recovery of muscle function in the late phase is associated with recovery of muscle mass or alternately whether weakness persists despite recovery of muscle mass. Answering this question would clarify potential mechanisms underlying persistent late-phase weakness. Unfortunately, since prehospital functional status of these patients is almost always unknown, it is difficult to know how baseline muscle function contributes to long-term functional outcomes. In many patients, the ‘failure to recover’ may reflect their baseline functional status pre-ARDS.

Prolonged metabolic disturbances and immune suppression have been described in survivors of burns [32] and sepsis [33]. The term post-intensive care syndrome has been used to refer to the constellation of psychiatric, cognitive, and physical function problems present in ICU survivors, including those with ARDS [34]. The relationship of systemic immunosuppression or hypermetabolism to late-phase skeletal muscle dysfunction in patients with ARDS deserves further attention.

Pharmacologic and nutritional contributions to early- and late-phase muscle wasting

Some of the earliest reports of muscle weakness in critically ill patients associated the presence of what is now

called ICUAW with both glucocorticoids and neuromuscular blockade (NMB) [35, 36]. However, more current evidence suggests that glucocorticoids, but not NMB, is associated with ICUAW [20, 23, 37]. In the most compelling recent evidence, a randomized controlled trial of the neuromuscular blocker cisatracurium for severe ARDS, the incidence of ICUAW, measured by MMT, at hospital discharge was no different from control [38].

The association of ICUAW with glucocorticoids appears stronger than that of NMB. Increased duration of glucocorticoid use is independently associated with increased myosin degradation in the skeletal muscles of critically ill patients on mechanical ventilation [39]. In the ARDS Network Long Term Outcomes study, which followed ARDS survivors enrolled in ARDS network trials, both dose of corticosteroid and ICU length of stay were associated with reduced functional outcomes at 6 and 12 months [20]. These results suggest that drugs or interventions in the ICU, even administered for short durations, can impact long-term outcomes. Other data supporting the importance of glucocorticoids in muscle wasting in ARDS include the fact that the glucocorticoid receptor is an upstream modulator of muscle ring finger 1 (MuRF1) activation [40], an important contributor to early-phase muscle wasting (see 'The ubiquitin-proteasome system and muscle ring finger 1' section). Overall, the available data suggest that both endogenous and exogenous glucocorticoids contribute to muscle dysfunction in ARDS.

The role of nutrition in muscle weakness in critical illness and its contribution to muscle wasting is controversial, although recent evidence suggests that increased caloric intake during the early phase does not prevent late-phase muscle dysfunction. In the long-term follow-up of patients with ARDS in the EDEN (early versus delayed enteral nutrition) trial, muscle functional outcomes were unchanged between the two arms at 6 and 12 months [6]. Emerging evidence suggests that early parenteral nutrition (PN) is detrimental for muscle function in these patients [41]. The currently available data suggest that early and full caloric nutrition, either enteral [42] or parenteral [41], does not reduce the incidence of ICUAW in critically ill patients, although future investigation is warranted. Nutritional factors may be more important for improving muscle mass when administered during the late phase.

Early- and late-phase muscle dysfunction in acute respiratory distress syndrome: underlying mechanisms

Mechanisms of early-phase muscle wasting

As mentioned above, the cardinal feature of early-phase muscle dysfunction is atrophy, driven by inflammation and disuse. The net balance of protein synthesis and degradation determines myofiber size. Therefore, atrophy can occur through increased protein degradation, reduced protein synthesis, or both. In most experimental models of muscle atrophy, increased muscle protein degradation - not reduced protein synthesis - accounts for the loss of muscle mass [43], although some controversy remains [44]. With regard to ARDS-associated muscle dysfunction, both increased protein degradation and reduced protein synthesis contribute to early-phase atrophy, although the former mechanism predominates. In the largest recent study measuring protein synthesis and degradation in critically ill patients (which included, but was not limited to, patients with ARDS), rectus femoris cross-sectional area decreased by 18 % over 10 days. In this study, patients in the early phase (day 1) showed reduced protein synthetic rates compared with fasted controls. At this time point, muscle protein degradation predominated over protein synthesis. By day 7, protein synthetic rate had increased compared with day 1 and fasted controls, likely an attempt of the muscle to recover from the massive protein degradation and atrophy during the inflammation-driven early phase, although the balance remained favoring ongoing atrophy [45].

In recent years, three major pathways have emerged as the primary regulators of muscle atrophy: the calpain-caspase system, the ubiquitin-proteasome system (UPS), and the autophagy-lysosome system (autophagy) [43, 46]. All have been implicated in inflammation and disuse atrophy, but their relative contributions and interrelationships during the early phase of muscle wasting in ARDS remain incompletely understood.

Inflammation-driven atrophy

Both pro- and anti-inflammatory cytokines are present in the lungs and plasma of patients with ARDS [47]. Many of these pro-inflammatory cytokines are associated with muscle atrophy in humans and rodents, including tumor necrosis factor-alpha [48], interleukin (IL)-6 [49], IL-1β, and others [50, 51]. Muscle atrophy occurring via inflammatory cytokines classically requires activation of the transcription factor NF-κB (nuclear factor kappa light chain enhancer of activated B cells) [52–54], which in turn can increase muscle protein degradation, leading to rapid limb and respiratory muscle myofiber atrophy.

In lung-injured mice, marked early muscle atrophy occurs along with lung inflammation [16]. NF-κB activation in skeletal muscle is necessary for initiating the muscle atrophy during this early phase [55]. These data suggest that systemic mediators, such as inflammatory cytokines or other soluble factors that activate NF-κB, are important in the early phase of muscle atrophy in ARDS. These muscle proteolytic pathways may exist in order to provide nutritional substrates to an organism under major stress, such as massive infection or injury. In addition to promoting muscle protein degradation, pro-inflammatory cytokines may promote atrophy through

inhibition of the pro-hypertrophy IGF-1/AKT pathway [56], although this concept has received less attention.

Disuse-driven atrophy

There is little doubt that disuse contributes to the limb muscle atrophy associated with ARDS, given the profound limb and diaphragm disuse that characterizes these patients. In fact, recent work suggests that bed rest may 'prime' skeletal muscle for atrophy by increasing the expression of muscle surface TLR4 (Toll-like receptor 4) receptors, which, when activated, can promote atrophy [57, 58].

However, both animal models and human data support the concept that muscle wasting associated with lung injury is phenotypically different from that induced by immobility alone. A recent report of healthy persons confined to bed rest for one week documented a 4 % loss of lean body mass [57]. In a study of critically ill patients on mechanical ventilation, muscle mass loss was approximately 12 % [45] over that same time period. Likewise, in an animal model of hind-limb immobilization, an approximately 5 % muscle mass loss of the tibialis anterior muscle was seen at day 3.5 [59], and we find an approximately 22 % muscle mass loss in the tibialis anterior of lung-injured mice at this time point [16]. Collectively, these data support the concept that disuse atrophy contributes to the early phase of wasting, but less so than inflammation-driven atrophy.

Molecular targets for attenuating muscle atrophy in the early phase

The ubiquitin-proteasome system and muscle ring finger 1 Animal models and emerging human data suggest that the UPS plays a prominent role in the early phase of limb and diaphragmatic muscle wasting in ARDS. We and others have shown that the UPS-mediated atrophy is prominent in the early phase of muscle wasting in lung-injured mice [16, 55, 60]. The E3 ligase MuRF1, which coordinates the ubiquitination of myosin heavy chain (MyHC) and other contractile proteins for proteasomal degradation [61], is necessary for early-phase atrophy in this model. Support for the importance of this mechanism in ICUAW is the finding that selective MyHC degradation is a salient pathologic feature of critical illness myopathy [62]. Others have shown that 20S proteasome activity is upregulated in the vastus lateralis of patients on mechanical ventilation, which was also associated with upregulation of the forkhead box o (FoxO) transcription factors, MuRF1, and other atrophy-promoting genes [39]. In recent work evaluating serial biopsies in mechanically ventilated patients, the only consistent change in protein expression was in MuRF1 and atrogin 1 expression, both of which were downregulated over time [45], supporting the observation that this pathway is activated in the early phase. Another study reported reduced MuRF1 levels in the muscles of critically ill patients, although the varying time points for muscle biopsies limit the interpretation of this finding [63]. The currently available human and animal data suggest that the UPS plays a prominent role in the early phase of muscle atrophy in ARDS. As therapeutic agents targeting proteins involved in UPS-mediated atrophy are developed and tested [64], their use in the early phase of ARDS-associated muscle wasting should be considered.

Autophagy Briefly, macroautophagy (autophagy) is a ubiquitous process present in multiple cell types in which cellular proteins and cytoplasm are degraded and recycled via lysosomes. A focus on autophagy in skeletal muscle is relatively underexplored [65]. Increased autophagic flux can cause atrophy, although inhibition of autophagic flux can also induce atrophy, potentially through upregulation of the UPS [65, 66]. Interestingly, both the UPS and autophagy pathways can be regulated by the same FoxO transcription factors [67].

Evidence suggests that autophagy is involved in ARDS-associated muscle wasting. Diaphragmatic disuse due to mechanical ventilation in brain-dead humans is associated with the rapid appearance of autophagosomes and autophagy-related genes and proteins [68]. This finding could be due to either increased flux or a block in distal autophagy processing. In a pig model (combining mechanical ventilation, endotoxin, NMB, and corticosteroids), significant limb muscle atrophy was associated with reduction in critical autophagy genes and proteins [69].

In a prospective study of 600 patients in the EPaNIC (Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients) trial, 122 of whom underwent muscle biopsy, those randomly assigned to late PN had a reduced incidence of ICUAW compared with those with early PN; this result was associated with an increased LC3II-to-LC3I ratio, a marker of autophagosome formation [41]. These data suggest that autophagy induction is associated with improved muscle function.

The role of autophagy during the early phase of muscle wasting in ARDS is complex, given that either accelerated or impaired autophagy may be deleterious to muscle function. Details regarding the role of autophagy and its relationship with the UPS are still emerging, and more work is needed to determine the role of autophagy in the early phase of muscle wasting in ARDS. Other types of muscle autophagy, including microautophagy [70] and chaperone-mediated autophagy [71], also deserve future investigation in this context.

Caspases and calpains Caspases and calpains are early mediators in the breakdown of sarcomeric proteins that

can then undergo degradation by the UPS or autophagy pathway. Caspases and calpains have been investigated more extensively in both endotoxin- and mechanical ventilation-induced diaphragmatic dysfunction but not (to our knowledge) in animal models of lung injury. Supinski and colleagues [72] showed that calpain, caspase, and proteasome activity are upregulated in the diaphragm of endotoxin-treated mice. Likewise, diaphragm calpain activation peaks early (24 h) in the cecal ligation mouse model of sepsis. Co-administration of eicosapentoic acid prevented the loss of specific force-generating capacity in the diaphragm and prevented calpain activation [73, 74]. Others have shown that mechanical ventilation in humans causes atrophy and increased caspase 9 activity in diaphragm fibers [75]. As such, calpains and caspases remain attractive potential targets for intervention in the early phase of muscle wasting.

Neuropathy and other pathologies as potential therapeutic targets in the early phase

As mentioned above, polyneuropathy is found in a subset of patients with ICUAW. Critical illness polyneuropathy affects distal axonal sensory and motor nerves, which may lead to myofiber atrophy and contribute to weakness independent of atrophy. Histologically, peripheral nerves with [76, 77] or without [78] axonal degeneration have been described. The polyneuropathy in patients without nerve degeneration has been proposed to be due to a transient negative shift in voltage dependence of sodium channel fast inactivation leading to reduced excitability of the nerve, demonstrated in both rats and humans [79].

Autonomic dysregulation, which may be present in many patients with severe critical illness, may also contribute to polyneuropathy [80]. With this in mind, there has been recent interest in using β-blockade in patients with septic shock [81] as a way to attenuate sympathetic over-activation. Interestingly, stimulation of skeletal muscle β receptors leads to muscle hypertrophy through stimulating protein synthesis [82]. Therefore, muscle function should be incorporated into clinical trial design of future investigations of β-blockade in critical illness.

Epineurial and endneurial vascular leak [83] causing nerve edema is another proposed mechanism. Hyperglycemia, often characteristic of severe critical illness, could further impair nerve or muscle microcirculation [84]. This hypothesis may explain why intensive insulin therapy has been associated with a reduced incidence of ICUAW [85, 86]. Interestingly, the glucose transporter-4 (GLUT4) receptor, which modulates glucose uptake into muscle, appears mislocalized in patients with critical illness myopathy [87].

Additionally, reduced muscle membrane excitability is a common finding on electromyographic studies [23]. A series of studies has shown impaired sarcoplasmic reticulum calcium handling and impaired sodium channels in muscles of denervated and steroid-treated rodents [88–90], but to our knowledge this has not been studied in the context of lung injury. Owing to altered metabolism or increased muscle fatigue, muscle mitochondrial injury [91, 92] sustained during the early phase may contribute to muscle dysfunction.

Molecular targets for attenuating muscle atrophy in the late phase

Ongoing active muscle proteolysis through increased protein degradation does not appear to be a major contributing factor of weakness during the late phase. The massive inflammation-induced protein degradation has subsided at this time point [16, 45]. Therefore, therapies directed at attenuating muscle proteolysis are less likely to benefit as much as when administered during the early phase.

In contrast, enhancing protein synthesis may be useful during the late phase. Two studies suggest that there is actually already increased protein synthesis in the late phase. One study showed muscle activation of the pro-synthesis AKT-mTOR-S6k (AKT-mammalian target of rapamycin-ribosomal protein S6 kinase) pathway of critically ill patients from muscle biopsies that were obtained predominantly in the late phase [63]; a second study showed increased protein synthesis in the muscles of critically ill patients at day 7 [45]. This may be a compensatory mechanism to recover from the early phase, and studies are needed to determine whether augmenting protein synthesis pathways can improve muscle mass during the late phase. Therefore, we propose that late-phase therapies to improve muscle mass focus on enhancing protein synthesis or other factors to enhance myofiber size, such as through the myostatin pathway [93].

Neuropathy and other pathologies as potential therapeutic targets in the late phase

Evidence suggests that denervation injury may persist into the late phase. In a cohort of mechanically ventilated critically ill patients, muscle biopsies at about day 12 revealed upregulation of the muscle acetylcholine receptor γ mRNA, a marker of muscle denervation [39]. Late-phase wasting may also exist due to persistence of some factors initiated during the early phase, such as disuse, nerve or NMJ injury, excitation contraction uncoupling, inflammatory myopathy, or mitochondrial dysfunction.

Additional targets during the late phase include enhancing muscle regeneration by targeting muscle stem (satellite) cell activation/repair [94]. Additionally, enhancing autophagy, as a way to 'clean up' the misfolded

proteins and other debris that accumulated during the early phase, may theoretically benefit.

Many questions remain about the relationship of the early phase to the late phase. For instance, is late-phase wasting due to persistent injuries sustained in the early phase or are the two phases mechanistically independent? Is late-phase wasting purely a reflection of a return to a pre-hospital level of reduced muscle function in patients with underlying neuromyopathies or sarcopenia? Answering these questions will clarify potential therapies to improve muscle function in ARDS survivors. Figure 2 illustrates potential clinical factors and mechanisms associated with early- and late-phase muscle wasting in ARDS.

Currently available therapeutic approaches

Insulin administration and tight glycemic control appear to reduce ICUAW [85], although this approach has been tempered with the results of the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Surviving Using Glucose Algorithm Regulation) trial, which suggested an increased risk of death in the tight glycemic control arm, possibly due to hypoglycemia [95]. Perhaps strategies that reduce hyperglycemia without the risk of hypoglycemia will reduce the incidence of ICUAW.

Currently, early mobilization/rehabilitation is the most readily available therapy for the attenuation of ICUAW. Evidence has demonstrated that early rehabilitation of critically ill patients is safe and has the benefit of improving other outcomes in addition to muscle strength [96–99]. Emerging evidence suggests that passive loading of the leg in a rat model of mechanical ventilation and paralysis prevented atrophy and degradation of myosin [100]. In a small study of mechanically ventilated critically ill patients, passive movement of the leg attenuated loss of specific force (but not atrophy) measured by single-fiber contraction [101]. We have recently shown that a model of early mobilization in lung-injured mice attenuates the MuRF1-mediated loss of muscle mass and force during the early phase, through an NF-κB-mediated mechanism [102]. This suggests that early mobility may attenuate the inflammation-induced atrophy in the early phase. As such, early mobilization (even passive movement) remains the best available therapy for critically ill patients to attenuate early- and late-phase muscle wasting in ARDS.

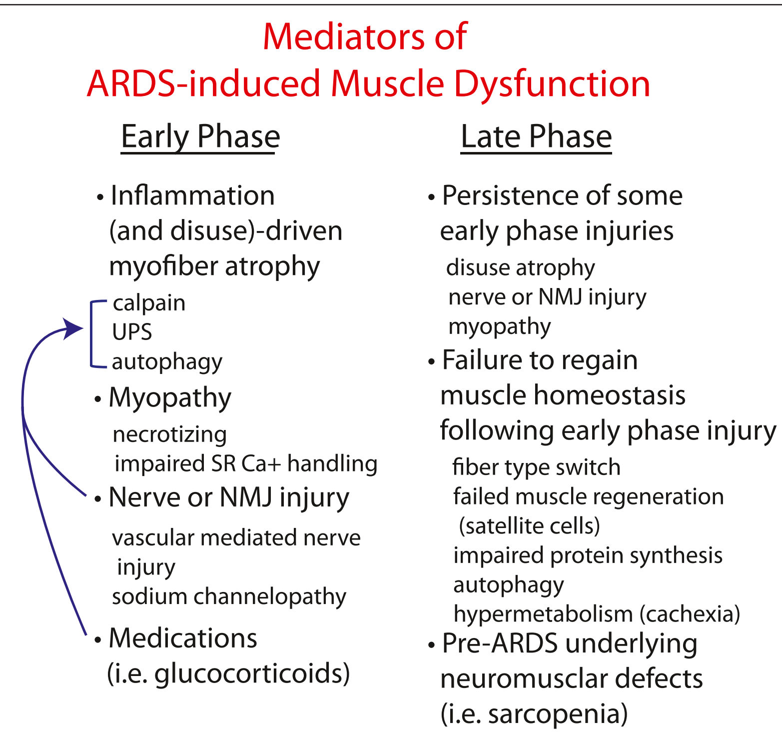

Fig. 2 Mediators of acute respiratory distress syndrome (ARDS)-induced muscle dysfunction. Skeletal muscle atrophy is the most universal feature of the early phase, which is driven fundamentally by inflammation and disuse. Other factors such as neuropathic injury and medications can exacerbate atrophy (blue arrow) and independently cause muscle dysfunction. Therefore, inhibiting muscle protein degradation is the most promising potential early-phase therapy. The late phase is marked by cessation of inflammation-induced muscle proteolysis and therefore potential treatments at this time point will differ. Mediators of the late phase may involve persistence of some early-phase injuries or a failure to regain muscle homeostasis following the early phase. Late-phase dysfunction may be compounded by underlying pre-ARDS neuromuscular defects. NMJ, neuromuscular junction; SR Ca^+, sarcoplasmic reticulum calcium; UPS, ubiquitin-proteasome system

Unfortunately, despite evidence that early mobility is safe and effective, there are limitations to its adoption, and implementation worldwide remains low [103, 104].

Neuromuscular electrical stimulation (NMES) may develop as an alternative therapy [105, 106], particularly for those who cannot participate in active physical therapy. In a small study, NMES attenuated type 2 myofiber atrophy, which was associated with relocalization of the GLUT4 receptor and improved glucose metabolism [87]. Further research is certainly warranted for this potential therapy.

Conclusions

As new therapies for inhibiting muscle protein degradation become available [64], it will be critical to administer them early in critically ill patients. As we propose that muscle atrophy is the most universal feature of ICUAW and that neuropathy will also lead to downstream myofiber atrophy, therapies that attenuate muscle protein degradation during the early phase have the highest theoretical benefit to improve in-hospital and long-term outcomes. Investigators interested in the early treatment of ARDS, such as the Prevention and Early Treatment of Lung Injury (PETAL) Network, could consider approaches that aim to attenuate the early phase of muscle wasting in patients with ARDS. This approach may open a new paradigm of therapies in ARDS, a syndrome that imparts a profound and lasting effect on the musculoskeletal system.

Abbreviations

AKT: Protein kinase B; ARDS: Acute respiratory distress syndrome; FoxO: Forkhead box o; GLUT4: Glucose transporter-4; ICUAW: Intensive care unit-acquired weakness; IGF-1: Insulin like growth factor 1; IL: Interleukin; MMT: Manual muscle testing; MuRF1: Muscle ring finger 1; MyHC: Myosin heavy chain; NF-κB: Nuclear factor kappa light chain enhancer of activated B cells; NMB: Neuromuscular blockade; NMES: Neuromuscular electrical stimulation; NMJ: Neuromuscular junction; PN: Parenteral nutrition; UPS: Ubiquitin-proteasome system.

Competing interests

The authors declare that they have no competing interests.

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